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III[me] CONGRES INTERNATIONAL D'ALLERGOLOGIE

PARIS, 19-26 octobre 1958

Rapports présentes au
III^me^ CONGRES INTERNATIONAL D'ALLERGOLOGIE

Proceedings presented at the
III^rd^ INTERNATIONAL CONGRESS OF ALLERGOLOGY

Kongressberichte vom
III^en^ INTERNATIONALEN KONGRESS FUR ALLERGOLOGIE

Ponencias presentadas al
III^r^ CONGRESO INTERNACIONAL DE ALERGOLOGIA

Edités par
Edited by
Herausgegeben von
Editado por

B N Halpern
et A Holtzer

Paris 1958

ÉDITIONS MÉDICALES FLAMMARION

NOMS ET TITRES UNIVERSITAIRES DES RAPPORTEURS

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Le III^e Congres International d Allergologie qui se tient a Paris sous le patronage de l Association Internationale d Allergologie et sous la presidence du Professeur FEINBERG reunit la repre entation de trente neuf nations

Les *Symposia* traitent de sujets qui dans l etat actuel de l Allergologie avaient besoin d etre éclairés

1° *Asthme et Emphysème* envisagés sous des aspects divers en particulier ceux de la pathogénie et de la physio pathologie le syndrome *Asthme* et le syndrome *Emphysème* devant etre mieux discrimines qu ils ne le sont actuellement

2° *Les propriétes physico chimiques des anticorps allergiques*

3° Les acquisitions récentes ur l *etiologie* et le *traitement des affections allergiques*

4° *Les aspects biochimiques* de l hypersensibilite

5° *L auto et l iso-sensibilisation*

6° *L eczema diathésique*

7° *Le retentissement social de l Allergologie dans les différents pays*

On ne saurait assez se féliciter que le professeur FEINBERG Presid nt du Comite Exécutif de l Association Internationale d Allergologie oit à la tete de cette importante manifestation internationale Il etait tout désigne par ses travaux sa notoriété mondiale ses relations avec les Allergologistes des divers pays

Le D^r HALPERN President du Comite d Organisation et M^me le D^r A HOLTZER Secretaire du Comite ont eu la lourde tâche de coordonner les rapports et les communications et de regler tous les details de ce Congres Qu ils en soient particulièrement remercies

PASTEUR VALLERY RADOT

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FOREWORD

by

SAMUEL M FEINBERG M D

Président International Association of Allergology
Nov 10 1955 — Oct 26 1958

It is not absolutely necessary that you read my remarks here But I sincerely believe that if you will spend the few minutes required to do so you will have a clearer perception of the overall nature and contents of the Proceedings as well as the setting of the Congress which it reports and the organization responsible for it

The Proceedings constitutes a report of the major presentations at the Third International Congress of Allergology The Congress is the official meeting of the International Association of Allergology and is sponsored by it with the collaboration of the Allergy Association of France Since the I A A and the Congress are synonymous in major aspects and since I have had the dual function of President of the I A A and Chairman of [illegible]

improve this exchange of knowledge between Congresses The I A A is an *association of national societies rather than individuals* Each national society which is a component member of the I A A is represented by one delegate whether it has a membership of 10 or 1 000 The House of Delegates aided by an Executive Committee is the governing body of the I A A

The Scientific Program of the Third International Congress of Allergology is composed of 3 parts short free papers small luncheon conferences symposia Only the Symposia have been published in the Proceedings

To better understand the published papers in the Proceedings it should be realized that large international congresses covering a large field of interests do not attempt to present definite and narrow research reports in such symposia Rather it has been found more fruitful for the participators to present a review or a bringing up to date of a broad phase of a subject With a variety of subjects presented it is rare indeed that the person in the audience will have covered in his reading all that the partici

pator will present Of course new data never yet published may also be included in the presentation

In preparing the Program of the Symposia certain principles have been kept in mind An attempt has been made to balance the clinical and practical with the basic and experimental Both in the clinical and the basic presentations a sincere effort was made to have something of value for almost all variations of interest in the field In addition to material of substance for the allergist one will find here areas of appeal to the internist pediatrician dermatologist surgeon physiologist immunologist biochemist public healt workers and others The subjects covered include asthma and emphysema biochemical aspects of allergy various developments along clinical lines atopic dermatitis antibodies auto and iso immune reactions and economic and social aspects They contain such divergent topics as the mechanism of emphysema the immunology of homotransplantation customs in practice of allergy in many parts of the world the relation of hypersensitivity to collagen diseases metabolic factors in topic d rmatitis m thods and results of pulmonary function techniques the role of histamine and histamine liberators a study of causes of death ain asthma insect dusts as common causes of allergy the role of immunology in common blood disorders advances in our knowledge of antibodies and many other subjects The Proceedings constitutes a valuable up to date cross section of allergy progress throughout the world

Virtually without exception the panelists presenting this program (and Proceedings) are outstanding authorities in their particular subjects Those who know well any particular field may find it strange that many many international authorities (some of greater repute than some of the present participants) are not represented here This is not because of ignorance on the part of the Program Committee Rather it has been due to a number of circumstances such as illness of the invited guest a conflict of other engagements accessibility of the desired guest limitations in overall financial resources to pay expenses and above all the limitations of time for the Program For example, the entire Congress and the Proceedings could have confined themselves to Auto Immune Reactions This would have enabled the Committee to place virtually all authorities on the Program However such a Congress would have an entirely different significance and appeal and would be composed of a rather specialized attendance

You may wonder about the wisdom of publishing the Proceedings *before* the Congress *It is admitted that if the Proceedings were published after* the Congress the presentations might be slightly more up to date (at the time they are presented) and if recorded as spoken (and edited by the speakers) would be more spontaneous On the other hand they would be less accurate Furthermore what is most important is that the Proceedings would probably be published about two years later or never Such has been my experience with authors and speakers Once they have spoken it is humanly understandable that they feel reluctant (after the show is over) to prepare or edit a manuscript for the Editor A Proceedings published after the Congress would be at least 2 years behind in developments

In connection with the preparation of the Program (which is the material

in the Proceedings) and other affairs of the I A A this writer has spent much time over a period of 3 years (the duration of his office) Much of that time was spent on the Program In the performance of these and other duties for the I A A I have been fortunate in having an outstanding [illegible] The Program Committee members [illegible] rnard N Halpern Dr Jose Quintero [illegible] vid Williams have been most helpful and energetic with their counsel and active participation Financial contributions (see list) have enabled us to invite a number of authorities from long distances The Symposium participants have been most cooperative in their willingness to abide by every necessary change (such as reduction of time allotted for presentation) The Symposia Chairmen have done much to complete their Symposia The Delegates and members of the Executive Committee have not only helped with their counsel but have given me wondefrul cooperation in promptness of response on many matters particularly on voting The various committees have been cooperative in all respects Of these special thanks are due to the Committee on Constitution and Nominating Committee and the Chairman of these Dr Howard Osgood Through his indefatigable efforts a number of changes in the Constitution designed to improve the efficiency of the I A A have been offered to the Delegates

If the administration has been successful and the Congress Program and Proceedings have contributed to international understanding and knowledge the major thanks are due to two loyal friends who have devoted their time energies and have made personal sacrifices for this goal Dr Jo e Quintero Fossas was to my mind the ideal Secretary General No amount of detail was too much for him no diplomatic obstacle was too big to hurdle Much of the systematic operation of the I A A is due to his efforts and sagacity His friendship and loyalty will always be cherished by me

I hope it will not embarrass him if I pay public tribute to my very dear friend Dr Bernard N Halpern As President elect he was kept busv by me with a round of correspondence involving himself and the Secretary General I sought his advice on all matters The President s administration was essentially a triumvirate As a member of the Program Committee he gave valuable suggestions and spent much effort As Chairman of the Organizing Committee of the Congress he had virtually a full time back breaking job And when it came to editing the Proceedings *naturally it fell to the lot of Bernard Halpern It* is truly his energy enthusiasm knowledge of various fields acquaintance with authorities diplomacy and persistence which have given vitality to the I A A and a successful Congress and Proceedings To my loyal and staunch friend go my admiration and respect and best wishes for sustained energy and good health to head an even more successful administration Under his leadership the I A A (and the next Congress) should augment its contribution to the field it represents

SYMPOSIUM I

Asthme et Emphysème
Asthma and Emphysema
Asthma und Emphysem
Asma y Enfisema

INTRODUCTION AU SYMPOSIUM « ASTHME ET EMPHYSEME » DISCRIMINATION NÉCESSAIRE ENTRE LES DEUX SYNDROMES

par

PASTEUR VALLERY RADOT

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Lorsqu on parcourt la littérature médicale ayant trait a l asthme on est frappe de constater trois faits

1° Les auteurs appellent souvent *asthme* des crises dyspnéiques qui n ont aucun rapport avec ce qu on doit denommer asthme ainsi en est il pour « l asthme cardiaque »

2° *Asthme pur* et *emphyseme primitif pur* sont souvent confondus on appelle a tort *asthmes* des syndromes qui relevent de l *emphyseme*

3° *Asthme intriqué* et *emphyseme associé* la plupart du temps ne sont pas discriminés aussi range t on souvent sous la denomination d *asthme intrique* ce qui rentre dans le cadre de l *emphyseme associé*

Il importe d établir ces distinctions et de n appeler *asthme* que ce qui releve de ce syndrome sans quoi les observations cliniques les statistiques et les épreuves fonctionnelles rapportées n ont aucune valeur

Dans cette Introduction au Symposium sur « asthme et emphysème » nous essayerons d établir la discrimination nécessaire entre les deux syndromes distinction trop souvent oubliée par les auteurs contemporains



ASTHME PUR ET EMPHYSÈME PRIMITIF PUR

Tout d abord il faut définir l *asthme pur*

Asthme pur

On ne doit appeler asthme qu un syndrome ayant les caracteres suivants acces de dyspnee paroxystique revenant a intervalles plus ou moins rappro

chés et ne laissant dans les périodes intermédiaires aucune trace. Pendant l'accès le thorax se bloque en inspiration. Le sujet s'efforce avec difficulté d'expirer l'air. A l'auscultation on constate une inversion du rythme respiratoire : l'inspiration est courte en même temps que humée, l'expiration est prolongée. La radioscopie révèle un emphysème accentué.

Bientôt l'hypersécrétion bronchique se traduit par des ronchus et des sibilances ; on entend ces râles bruyants à distance. Le malade est cyanosé par suite de l'augmentation du taux du CO_2 alvéolaire.

Puis apparaissent des crachats épais et filants, translucides ; au microscope on y trouve de nombreux éosinophiles.

Après cette expectoration l'asthmatique commence à se sentir libéré. Petit à petit la crise cède et tout revient à la normale.

La crise d'asthme est de causes variées, presque toujours d'origine externe, parfois d'origine interne. Un processus allergique dans la majorité des cas la conditionne.

La dyspnée de la crise d'asthme est due à une diminution du calibre de la lumière bronchique. Ce bronchospasme est bien visible à la bronchoscopie comme l'ont montré encore récemment les observations endoscopiques de Dubois de Montreynaud. Lorsqu'il s'agit d'un asthme allergique, au spasme des bronches s'ajoute un œdème considérable de la muqueuse bronchique (Pasteur Vallery Radot, Halpern, Dubois de Montreynaud).

Des phénomènes sécrétoires s'associent au bronchospasme (et à l'œdème quand il existe).

Ces différents obstacles sur les conduits aériens conditionnent l'emphysème aigu.

La crise d'asthme terminée, le sujet peut rester des jours, des semaines, voire des mois et plus sans avoir une nouvelle crise. Ainsi en est-il par exemple dans l'asthme d'origine équine ; si l'asthmatique sensibilisé n'est plus en contact avec des chevaux, il ne fait pas de crise ; mais approche-t-il de nouveau un cheval, presque immédiatement une crise réapparaît.

Dans l'intervalle des crises, le sujet ne présente aucun trouble respiratoire ; l'auscultation ne révèle aucun râle ; la radioscopie du thorax est normale. L'effort même ne réveille aucune dyspnée. L'exploration fonctionnelle de la ventilation pulmonaire ne décèle aucune anomalie. Le diagnostic de l'asthme dans ces périodes intermédiaires ne peut se faire que par l'anamnèse.

Si les crises, au lieu d'être espacées, se renouvellent fréquemment, on pourra observer entre elles une « amorce » d'emphysème (dont nous verrons l'explication plus loin) se traduisant par une insuffisance respiratoire que décèle seul un *fond dyspnéique latent* révélé par la mesure du *débit expiratoire moyen* défini par le rapport entre la quantité d'air expiré et la durée de l'expiration lorsqu'on demande au sujet de faire une expiration forcée (Jean Hamburger).

Emphysème primitif pur

L'*asthme pur* ainsi caractérisé ne saurait être confondu avec l'*emphysème primitif pur*, apparaissant chez un sujet sans passé pulmonaire

Cette affection survient d ordinaire chez un homme apres la cinquantaine Il s agit d une lésion primitive caractérisée par une atteinte degénérative du systeme élastique pulmonaire les alvéoles ont perdu leur élasticité d ou leur distension apres l inspiration le tissu pulmonaire ne revient plus sur lui meme

Le sujet qui en est atteint se plaint *au debut* d une dyspnée n apparaissant qu à l effort On le prend souvent d emblée pour un cardiaque mais on constate que l auscultation du cœur est normale la T A est normale la radioscopie du cœur et l électrocardiogramme ne révelent aucune anomalie

A ce stade l examen clinique du poumon et la radioscopie pulmonaire peuvent ne pas renseigner Seules les epreuves fonctionnelles respiratoires peuvent etre révélatrices

Diagnostic entre asthme et emphysème au début

Le diagnostic entre *asthme* et *emphysème* est facile et cependant bien souvent on confond l un et l autre dans les publications

Les acces de dyspnée paroxystique qui parfois se produisent a l effort peuvent rendre le diagnostic difficile entre *asthme vrai* et *accès de dyspnée paroxystique chez un emphysemateux* Mais trois symptomes cliniques sont en faveur de l emphyseme

1° l absence d expectoration 2° l apparition des acces uniquement à l effort 3° la tres courte durée des acces

Dans les cas douteux on s appuiera sur la recherche de l *éosinophilie sanguine* elle existe dans 75 p 100 des cas d asthme comme nous l avons montré avec P Blamoutier et François Claude mais il faut éliminer les autres causes d éosinophilie en particulier les parasitoses

Récemment R Tiffeneau a proposé la *recherche de la mesure de l excitabilité acétylcholinique du poumon* D apres R Tiffeneau chez tous les asthmatiques existe une sensibilite exagerée du poumon vis a vis de divers agents excitants acétylcholine en particulier On recherche le *seuil d excitabilité acétylcholinique du poumon* lequel s exprime par la plus petite dose d acétylcholine (administree par la voie aérienne sous forme d aérosols) dite *dose liminaire* capable de produire un effet ventilatoire spirographiquement tangible diminution du volume ventilatoire maximum (capacite vitale) et du volume expiratoire maximum seconde (capacité pulmonaire utilisable à l effort)

D apres Tiffeneau le diagnostic différentiel entre l asthme et l emphyseme est facilite par les donnees pneumospirographiques et par la recherche de l excitabilité acétylcholinique du poumon les premieres précisent l emphyseme et son degré la seconde l asthme

Évolution de l emphyseme

L emphysème apres le stade de début evolue La dyspnée devient permanente avec exageration prononcée a l effort Alors les signes cliniques et radiologiques sont tres nets A l examen le thorax est distendu globuleux l extension de la cage thoracique est extremement diminuee peut meme etre presque nulle a la percussion on constate une hypersonorité qui va parfois jusqu à faire disparaitre la matite cardiaque et la matité hépatique

à l auscultation l inspiration est courte l expiration lente et prolongée on entend — mais non toujours — des sibilances A la radioscopie les cotes ont tendance à être horizontales le diaphragme est abaissé les deux champs pulmonaires montrent une hyperclarté le thorax est distendu meme en expiration

Les explorations fonctionnelles mettent en évidence l emphyseme et son degré Parmi les différentes épreuves proposées il faudra avant tout utiliser celles qui révèlent l augmentation de l air résiduel et le ralentissement de la vitesse expiratoire (mesurée sur une courbe spirographique) ces deux signes sont les caractéristiques essentielles de l emphyseme

A vrai dire l emphyseme à ce stade est de diagnostic facile Il ne peut être confondu avec l asthme et c est pourtant ce qui se constate bien souvent surtout quand l emphyseme est accompagne de crises dyspnéiques

ASTHME AVEC EMPHYSÈME SECONDAIRE

Un asthmatique dont les crises sont très fréquentes développe très souvent un emphysème Il n est plus question ici de l emphyseme aigu qui accompagne la crise d asthme il s agit d un *emphyseme permanent* du probablement aux sténoses bronchiques répétées qui se sont produites au cours des crises d asthme

Le malade se présente comme un emphysémateux C est seulement à l interrogatoire qu on apprend que les crises d asthme ont precédé de plusieurs mois de plusieurs années l emphyseme On ne pourra donc confondre cet *asthme avec emphyseme secondaire* et l *emphyseme accompagné de crises asthmatiformes* Et cependant que de fois les auteurs confondent ces deux syndromes!

ASTHME INTRIQUÉ ET EMPHYSÈME COMPLIQUÉ

Tres souvent on se trouve en pré ence d un malade qui presente une dyspnée plus ou moins continue avec crises paroxystiques de type asthmatique Tout effort lui est pénible parce que cet effort si minime soit il exagere considerablement la dyspnée A cette dyspnée s ajoutent une infection bronchique et souvent une sclérose pulmonaire

L auscultation revelant des sibilances d intensite variee associées a des rales sous crepitants aux bases la constatation de crachats mucopurulents (quelquefois très abondants quand existe une dilatation des bronches) souvent accompagnés d une fievre légere la radioscopie thoracique montrant des hiles tres charges ou une sclerose fine disséminée dans les deux champs pulmonaires autant de signes qui permettent facilement d établir le diagnostic syndromique Mais on hesite entre *asthme intrique* ou *emphyseme complique*

Asthme intriqué

L *asthme intriqué* est tres fréquent Il s agit de sujets qui au début de leur affection ont eu un asthme pur puis les crises devenant très rapprochées parfois subintrantes a l emphyseme qui a compliqué l asthme se sont ajoutes

des signes de bronchite et à la radioscopie des manifestations de sclérose pulmonaire. D'autres fois il s'agit d'asthme d'origine infectieuse : c'est une surinfection bronchique qui a provoqué l'asthme, puis l'emphysème, enfin la sclérose pulmonaire.

Emphysème compliqué

L'*emphysème compliqué* est beaucoup plus fréquent que l'emphysème pur. Il s'agit parfois d'un emphysème primitif auquel se sont associées secondairement bronchites et sclérose pulmonaire. Beaucoup plus souvent il s'agit de bronchite chronique émaillée de poussées bronchitiques, particulièrement pendant la période hivernale ; à ces manifestations bronchitiques s'ajoute de l'emphysème.

A une période avancée de ces emphysèmes compliqués, l'insuffisance cardiaque n'est pas rare, se traduisant avant tout par un gros foie douloureux, symptôme qui caractérise le « cœur pulmonaire chronique ».

Rist a voulu expliquer l'emphysème accompagnant les bronchites à répétition par les efforts de toux qui provoquent une distension des régions apicales et parasternales, d'où emphysème localisé. Cet emphysème amoindrissant la capacité respiratoire totale oblige le sujet à approfondir ses inspirations au moindre effort et à distendre ses bases pulmonaires. « L'emphysème est alors généralisé. Il s'est constitué en deux étapes et il a fallu pour cela des années » (Rist).

Une autre pathogénie, beaucoup plus simple, peut être envisagée : le trouble de la ventilation secondaire à la sécrétion et à la tuméfaction bronchique provoque la distension des alvéoles pulmonaires.

Diagnostic entre asthme intriqué et emphysème compliqué

Devant ces malades présentant ce syndrome : *emphysème + crises d'asthme + infection bronchique*, auquel s'associe souvent une *sclérose pulmonaire*, la question qui se pose est la suivante : S'agit-il d'un asthme intriqué ou d'un emphysème compliqué ?

C'est uniquement par l'histoire clinique que le diagnostic pourra être établi. Le malade a-t-il eu au début de son affection des crises d'asthme pur : il s'agit d'asthme intriqué. A-t-il eu au début des signes d'emphysème ou bien des infections bronchiques à répétition qui se sont accompagnées ultérieurement d'emphysème : il s'agit d'emphysème compliqué.

Malheureusement bien des auteurs ne font pas cette discrimination entre asthme et emphysème et bien souvent ils appellent *asthmes intriqués* des *bronchites compliquées d'emphysème*.



CONCLUSION

Asthme et emphysème sont souvent confondus à tort. Il faut discerner l'un et l'autre syndromes par une étude clinique attentive.

RÉSUMÉ

L auteur montre que bien souvent dans la littérature médicale sont confondus asthme et emphysème Une distinction entre les deux syndromes doit être établie On ne doit appeler *asthme* que ce qui relève de ce syndrome sans quoi les observations cliniques les statistiques et les épreuves fonctionnelles rapportées n ont aucune valeur

L auteur s efforce d établir cette distinction Apres avoir défini l *asthme pur* et l *emphysème pur* il montre que le diagnostic est facile et cependant les deux syndromes sont parfois confondus parce que des acces de dyspnée paroxystique qui se produisent a l effort même dans l emphysème au début peuvent amener la confusion

L emphysème évolué avec ses signes caractéristiques et ses troubles de l exploration fonctionnelle pulmonaire est de diagnostic facile et cependant il est parfois pris a tort pour de l asthme

L asthme avec emphysème secondaire doit être distingué de l emphysème primitif ce qui peut être parfois ardu lorsqu on ne connait pas l histoire de la maladie

Tres souvent on se trouve en présence d un malade qui présente une *dyspnée plus ou moins continue avec crises paroxystiques de type asthmatique* Tout effort lui est penible parce que cet effort si minime soit il exagere considérablement la dyspnée A cette dyspnée s ajoutent une infection bronchite et souvent une sclerose pulmonaire Ici le diagnostic est souvent malaisé entre *asthm intriqué* et *emphysème compliqué* C est par l histoire cliniqu que le diagno tic peut être établi Malheureusement bien des auteurs ne font pas cette discrimination entre *asthme intriqué* et *emphysème compliqué* et bien des travaux intitulés « asthme intriqué » traitent en réalite de *bronchites compliquées d emphysème*

SUMMARY

The author points out that in medical litterature asthma and emphysema are often confused with one another

A discrimination between the two syndroms should be made

When referring to *asthma* one should only include what strictly belongs to this syndrom otherwise reported clinical records statistics and functional tests are valueless

The author s aim is to emphasize this discrimination After giving definition of *pure asthma* and *pure emphysema* the author shows that diagnosis is generally easy however the two syndroms are sometimes confused on accoun of the paroxysmal character of the dyspnea occuring during effort even in beginning emphysema

Chronic emphysema with it s characteristic symptoms and it s distubances of the pulmonary function is easily diagnosed but is nevertheless sometimes mistaken for asthma

Asthma with secondary emphysema must be distinguished from primary asthma which may be sometimes difficult unless one knows the history of the disease

Very often one deals with a patient suffering from more or less continuous dyspnea with *paroxysmal outbursts of the asthmatic type* To him all efforts are exhausting because the slightest effort greatly increases the dyspnea Very often the dyspnea is associated with a bronchial infection and pulmonary sclerosis

In such cases it is sometimes difficult to diagnose *intricated asthma* or *complicated emphysema* Only the clinical history can help in the differenciation of the two syndroms

Unfortunately many authors do not make this discrimination and many publications concerning intricated « involved asthma » deal as a matter of fact with « bronchitis with chronic emphysema

ZUSAMMENFASSUNG

Wie der Autor zeigt werden in der medizinischen Literatur oft die Begriffe Asthma und Emphysem verwechselt Man soll zwischen den beiden Syndromen unterscheiden Man darf den *Namen Asthma nur dem* betreffenden Syndrom geben da sonst die Berichte uber klinische Beobachtungen statistiche Daten und Funktionsprufungen keinerlei Wert besitzen

Der Autor betont die Notwendigkeit diese Unterscheidung zu treffen Nach der Definition des *reinen Asthmas* und des *reinen Emphysems* zeigt er dass die Diagnostik leicht ist und indessen die beiden Syndrome doch bisweilen miteinander verwechselt werden da Anfalle von paroxysmaler Dyspnoe wie sie bei Anstrengung auch am Beginn eines Emphysems autreten Verwirrung stiften konnen

Das voll *ausgebildete Emphysem* mit seinen charakteristischen Merkmalen und seinen Storungen der Atemfunktionsprufung wird leicht diagnostiziert und doch wird es bisweilen zu Unrecht als Asthma angesehen

Das *Asthma mit einem sekundarem Emphysem* muss von einem primaren Emphysem unterschieden werden was manchmal schwierig sein kann wenn man die Krankheitsanamnese nicht kennt

Oftmals sieht man einen Patienten der eine mehr oder weniger kontinuierliche Dyspnoe mit paroxysmalen Krisen vom Asthma Typus zeigt Jegliche Anstrengung ist fur ihn beschwerdlich da auch die kleinste Anstrengung die Dyspnoe betrachtlich verschlimmert Dieser Dyspnoe kann sich eine Bronchialinfektion und oft eine Pulmonarsklerose anschliessen Nun ist die Diagnose oftmals schwierig zwischen *Misch Asthma* (asthme *intrique) und komplizierten Emphysem (emphysème complique)* Mit Hilfe der klinischen Anamnese kann hier die Diagnose gestellt werden Ungluckseligerweise treffen viele Autoren nicht eine Unterscheidung zwischen *Misch Asthma* und *kompliziertem Emphysem* und viele der als Arbeiten uber *Misch Asthma* bezeichneten Publikationen handeln in Wirklichkeit von *mit Emphysem komplizierten Bronchitid n*

RESUMEN

El autor muestra que en la literatura medica asma y enfisema se confunden a menudo Debe establecerse una distinción entre ambos síndromes No debe llamarse *asma* nada mas que a lo que tiene las características de este síndrome sin lo cual las observaciones clínicas las estadísticas y las pruebas funcionales carecen de valor

El autor se esfuerza en establecer esta distinción Luego de definir el *asma puro* y el *enfisema puro* señala que si bien el diagnóstico es facil ambos síndromes son confundidos a veces y que la causa de esta confusion reside en los accesos de disnea paroxística que se producen durante el esfuerzo en los comienzos del enfisema

El *enfisema evolucionado* con sus signos caracteristicos y sus trastornos de la exploración funcional pulmonar es de diagnóstico fácil y sin embargo algunas veces es diagnosticado como asma

El *asma con enfisema secundario* debe ser diferenciado del enfisema primitivo lo cual puede ser difícil si no se conoce bien la historia de la enfermedad

Muy a menudo uno se encuentra en presencia de un enfermo que presenta una disnea mas o menos continua con crisis paroxísticas de tipo asmático Cualquier esfuerzo le resulta penoso porque por mínimo que sea exagera considerablemente su disnea A esta disnea se agregan una infección bronquial y a menudo una esclerosis pulmonar En estos casos el diagnóstico es frecuentemente difícil entre *asma intrincado* y *enfisema complicado* y es por la historia clínica que puede ser establecido Desgraciadamente muchos autores no hacen esta discriminación entre *asma intrincado* y *enfisema complicado* y numerosos trabajos sobre « asma intrincado » se refieren en realidad a bronquitis complicadas con enfisema

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FISIOPATOLOGIA DEL ASMA

por

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La secrecion del asma de otros tipos de disnea se hizo ante todo por su carácter accesional (mal cad pulmonum) Esta forma paroxística de pre sentarse ha continuado siendo considerada una peculiaridad principal frente a procesos orgánicos del aparato respiratorio Sin embargo poco a poco se ha ido obteniendo la convicción de que un cuadro similar puede implantarse sobre una enfermedad orgánica respiratoria o circulatoria (asma sintomatico o reacción asmoide vers asma primario) Amisismo se ha hecho evidente que no siempre el asma se manifiesta en esa forma recor tada accesional sino que se exhibe a veces con un cuadro clínico de estado disneico prolongado menos violento pero persistente y tambien con acen tuaciones intermitentes pero sin recuperación total en los intervalos en los que la sintomatología no difiere de la que arroja el enfisema pulmonar Formas puramente enfisematosas sin crisis o con crisis atenuadas del asma fueron descritas por Schwenckebecher Sergent nosotros y otros varios AA

Otro carácter distintivo que ha ido progresivamente subrayandose y cuyo analisis ha permitido grandes progresos en la etiología y tratamiento ha sido la frecuente dependencia de las crisis asmaticas de factores exógenos (estación clima profesion etc) explicables hoy por la acción sensibilizante de alergenos especiales que suponen esas circun tancias El papel que en la *provocación de las crisis tienen los choques antigeno anticuerpo la alergia* en su sentido estricto aparece seguro en una cierta proporcion de casos Ciertas otras influencias desencadenantes (climáticas fisicas psiquicas) no han podido ser explic das bajo el circulo de los fenomenos alergicos en el sentido citado del choque antígeno anticuerpo Tanto estas influencias como las modificaciones radicales en la reaccion frente a tales estimulos alergenos o de otra indole que suceden en virtud de circunstancias even tuales tales como la edad factores endocrinos fiebre embarazo etc indican que en la anormal dinámica reactiva juegan un papel esencial numerosos factores modificantes

En la evolucion clinica del asma puede advertirse como los caracteres de

la crisis varían se hacen modificaciones en la situación de intervalo y pueden presentarse complicaciones en el aparato respiratorio y circulatorio y en otros órganos lo cual constituye otro de los aspectos más interesantes de la fisiopatología del asma bronquial

Estos son los ángulos desde los que me propongo tratar la fisiopatología del asma por parecerme los que mayor interés ofrecen a nuestra consideración *a*) la dinámica respiratoria en el asma sus caracteres y factores de modificación *b*) su mecanismo y *c*) naturaleza de los cambios en el cuadro clínico y complicaciones en el curso ulterior del asma

I CARACTERES Y FACTORES DE MODIFICACIÓN DE LA MECÁNICA RESPIRATORIA EN EL ASMA

Los aspectos clínicos de los accesos asmáticos son diferentes de unos casos a otros y en cada uno de unos a otros momentos Hay no obstante algo de común sobre lo que debe recaer nuestra atención para definir en qué consiste en el sentido neumodinámico Ulteriormente podrán explicarse las diferencias de unos a otros tipos en virtud del predominio eventual de unos sobre otros factores Este conjunto de fenómenos que caracterizan al asma en sus fases sintomáticas integran lo que hemos llamado la « reacción asmática » Debemos ante todo reconocer que la «reacción asmática» no es privativa del asma bronquial primario procesos orgánicos del aparato respiratorio desde el enfisema y bronquitis al cáncer bronquial pueden originar fenómenos similares indistinguibles en el sentido de la mecánica respiratoria de la crisis propia del asma primario en enfermedades circulatorias pueden también darse paroxismos que no son en esencia sino la misma « reacción asmática » Por esto la describimos en sus caracteres peculiares reconociendo que tal reacción puede serlo todo como ocurre en el asma no complicado o puede ser sintomática es decir « inscrita » en una enfermedad orgánica circulatoria o respiratoria de la cual es solamente un fenómeno sintomático Al clínico corresponde conocer la « reacción asmática» como tal y como base para un tratamiento y en seguida distinguir si es primaria o inscrita y en cada caso cuáles son sus mecanismos de producción

El estudio de la función respiratoria en la clínica iniciado por Hutchinson al medir la capacidad vital y Waldemburg midiendo la presión espiratoria fué sobre todo aplicado a un análisis de sus modificaciones en las enfermedades por Minkowski y colaboradores Morawitz y Siebeck Stahelin y Schutte, hasta 1912 Rohrer en 1915 hizo una contribución fundamental con la medida de la resistencia de corriente en las vías aéreas y Neergard y Wirz (1927) aplicando la neumotacografía para medir la elasticidad pulmonar S v Leuwen aplicó la roentgenquimografía al análisis de la función respiratoria Christie inscribió la presión intrapleural como expresión de la presión intratorácica Jiménez Díaz y Sánchez Cuenca estimaron por primera vez los gases de la sangre arterial venosa y del ventrículo derecho Anthony Knipping y los grupos de Hurtado Christie y nosotros hicieron (1930 1939) estudios de la dinámica respiratoria ventilación de la sangre en el asma enfisema y fibrosis pulmonares Cournand y cols al introducir

en sus estudios sistemáticos el sondaje cardíaco y creando nuevos métodos de estudio de la función cardio-respiratoria inauguraron una nueva época. Las contribuciones fundamentales de Vuilleumier Rossier Tiffenau Otis Rahn y Wyss Lowell Fry Baldwin Fowler Gaensslen los grupos de Segal Comroe Mead Chemiack etc han ido ampliando las posibilidades de exploración y con ello los límites de estudio de la fisiopatología cardio respiratoria con la ideacion de nuevas técnicas de medida utilizando modernos metodos físicos y de integración matemática. Ha contribuído sin duda de modo valioso el estudio del asma experimental en los animales (Kallos y Pagel Neely nosotros y Wyss y cols Noelps Eschehager y Noelp) bajo los aspectos físico histológico y neumodinámico Asimismo ha sido de gran importancia la provocación experimental de la crisis por invec ción aerosol o cámara cerrada en el hombre normal y asmático de drogas provocadoras (ésteres de colina histamina serotonina) o de alergenos específicos (Chemiack Shrerrer y cols)

Los caracteres de mayor resalte en la clínica de la reacción asmática son la insuflación del tórax con elevación de la posición media y la espiración difícil incompleta y con poca fuerza En los estudios espirográficos de hace 20 30 años estos caracteres pudieron ser fácilmente objetivados (Anthony Hartwich Neergard y Wirz Hurtado y cols Hochrein nosotros etc) En la neumotacografía pudo subrayarse la existencia de dos fases en la *espiracion* una primera más rápida y una segunda más lenta y débil en la que el flujo llega a O aun con una presión intratorácica positiva El mismo fenómeno ha sido tambien visto en el asma experimental (v Wyss y cols Noelp y Noelp)

La medida de la presion del choque espiratorio sobre un manómetro metálico a traves de una máscara o pieza bucal (Plech) o con un aparato comm el manómetro de Hadorn Wyss permite objetivar este transtorno de modo rápido

La *insuflacion* del tórax el otro fenómeno de gran resalte clínico se con firma en el estudio de las fracciones del aire pulmonar así como en el estudio radiológico Hurtado y cols idearon un método radiológico de esti mar el volumen del pulmón por planimetría sobre las placas que nosotros también aplicamos Hofbauer propuso un sencillo diagrama del pulmón que también da rápidamente idea de la posición del tórax El estudio de las fracciones permite objetivar cómo la respiración circul nte se hace dentro de la reserva inspiratoria (aire complementario) y con aumento del volumen pulmonar al final de la espiración corriente (aire de reserva y residual) El volumen total del pulmón se eleva algo o puede ser el mismo (nosotros Baldwin y *cols*)

Nuestras mediciones fueron anteriormente hachas por el metodo del O_2 de Christie y posteriormente sumando la reserva funcional y el aire residual medidos en circuito abierto segun Richards y Cournand Hemos utilizado el espirometro de Collins con el ventilógrafo de Reichert Ulti mamente nuestros colaboradores han utilizado el método pletismográfico de Du Bois y cols

La elevación de la *posicion media* aunque tenga el inconveniente de la mayor dilución en espacio muerto del aire inspirado ofrece ventajas diná micas estando la elasticidad disminuida porque permite poner mejor en juego la reaccion elástica del pulmón y disminuir la probabilidad del colapso

espiratorio de los bronquios finos (Baldwin Dayman) la insuflacion y el abreviar el tiempo de espiración no haciendola a fondo defiende al enfermo en las crisis de dicho colapso que aumenta la resistencia al flujo primero y llega a la obstrucción en seguida De aquí que la frecuencia respiratoria en las crisis tenga un comportamiento distinto Intervienen en ella varios factores intensidad de las crisis grado de obstáculo en las vias aéreas emotividad etc En los niños y en las personas nerviosas en las primeras crisis predominan los casos con taquipnea En crisis mas fuertes en el adulto y en el asmático que subsconcientemente ha ido aprendiendo a aumentar la eficacia de su respiración predominan las formas con menor frecuencia respiratoria Todos los factores de la reacción asmática descenso de la compliance rigidez pulmonar obstáculo al flujo se acentuan en efecto de modo notable al aumentar la frecuencia respiratoria (Mead y cols Cherniack Sherrer y cols)

La *capacidad vital* (V C) en los asmaticos en los intervalos de las crisis puede normalizarse o si la crisis no ha totalmente remitido o en el asma antiguo aparecer disminuida En la crisis su disminución es muy evidente aunque difícil de medir con exactitud pero lo que fundamentalmente padece es *la maxima capacidad ventilatoria* (M B C) o Atmgranzwert (valor límite de respiración) introducida en la exploracion por Hermansen y Knipping Tiffenau demostrando que la limitación deriva de la dificultad espiratoria ideó la medida del aire espirado en el primer segundo despues de una espiración máxima es decir *del % de la V C espirado* en ese tiempo este valor ha sido medido con diferentes tecnicas (timed V C % T V C índice de flujo Gaenslen neumotacografía Beddell y cols Proctor y Wyss) Comparando las modificaciones de la V C M B C y T% V C se ve que este es uno de los caracteres más importantes de la r asmatica de fácil estimación en la clínica. También le rapidez inspiratoria está afecta aunque mucho menos como puede verse midiendo el % de la C V en el primer segundo que siendo de 90 en el normal puede disminuir hasta 65 % (v Wyss)

Dos factores la insuflación y el *secuestro* (trapping) del aire inspirado contribuyen a la elevación de respiración en espacio muerto Medido por la fórmula de Bohr en % de aire circulante nosotros no hallamos en el sujeto normal valores superiores al 30 % Su elevación en el asma puede ser considerable (Lowell Rossier y Scherrer etc) La ventilación (V^e 1) expresada en litros de aire ventilado por cada 100 c c de O aportado puede ser normal aunque puede disminuir en las crisis fuertes, dependiendo ello del « trapping » y el aumento del espacio muerto así como de la inhomogeneidad del reparto

Nosotros hemos utilizado para su estimación la medida del flujo y el analisis directo en el aparato de Scholander El consumo de O en el sujeto normal es así alrededor de 250 c c l y la eliminación de CO de 250

La *inhomogeneidad de distribucion del aire* en los pulmones que en un cierto grado ocurre en el sujeto normal se acentua de modo considerable en el asma como en el enfisema Fue objetivada por Briscoe y cols con helio y analizada por Darling y cols por la medida de la eliminación de N despues de respirar O 100 % que es el metodo utilizado por nosotros otros AA han utilizado el N meter de Lilly Uno de los factores limitantes de la ventilacion de la sangre en el asma es esta inhomogeneidad que traduce

la existencia de zonas bien perfundidas por sangre pero mal ventiladas, la mezcla de sangre procedente de estas zonas con la de otras bien ventiladas origina el cuadro de hipooxia en la sangre arterial con descenso del contenido en CO (hipooxia hipocapnia) ya apreciada por nosotros e interpretada en esta forma en nuestros antiguos trabajos Cuando se mide elasticidad estatica puede motivar errores debido a plenificarse territorios antes no aireados haciendo disminuir la presión para el mismo volumen

El estudio de *la elasticidad* principalmente ha sido realizado en el enfisema pero también en el asma Aunque no sean totalmente iguales el sentido paralelo de sus variaciones permite utilizar como medida de la presion intratorácica y por lo tanto de la presión intraalveolar la presión intraesofágica lo cual ha facilitado el analisis clinico de la elasticidad y sus factores por combinación con la estimación del volumen Los cambios de volumen para cada presión en distintas fases del ciclo respiratorio nos permiten medir las dos vertientes de la elasticidad distensibilidad del pulmón por el grado de aumento de volumen para cada momento de presión en la inspiración (« compliance » en la actual terminologia) y su recíproca la reacción de descenso de volumen para cada disminucion espiratoria de presión (elastancia) La amplitud de distension retracción dependen en la práctica de este factor reacción elástica y de las resistencias opuestas al vaciamiento y plenificación cuyo conjunto « resistencia » deriva a su vez de dos factores la viscosidad de tejidos (llamada viscancia por Bayliss y Robertson) y la resistencia bronquial al flujo de aire por su luz

Diferentes metodos han sido utilizados para estimar estos 3 factores compliance propiamente dicha resistencia viscosa y resistencia bronquial La medida del flujo y su presión por los métodos tacograficos la presion alveolar por el de Vuilleumer o sus modificaciones (Otis y Proctor Jeker y v Wyss) (que arroja por la inhomogeneidad de mezcla valores excesivos de viscosidad y bajos de resistencia bronquial) o por aparatos mas perfectos (pletismógrafo del cuerpo Du Bois y cols etc) o bien el registro de la presion intraesofágica La combinación de estos métodos permiten estimar la relación presion volumen y el trabajo respiratorio

En la respiracion normal la *presion alveolar espiratoria* e inspiratoria no presentan prácticamente diferencia esta es en cambio manifiesta en la crisis asmática en la que la presión intratoracica espiratoria puede estar muy aumentada Mas de tres veces aun para la misma frecuencia y volumen respiratorio han visto Scherrer y cols acentuarse esta diferencia en el momento de la crisis La medida e integracion de *la relacion presion volumen* han permitido demostrar (Mead y cols Cherniack) la rigidez funcional del pulmón en el asma que corresponde al carácter señalado por nosotros hace años de la reacción asmática como « insuflacion rigida » del pulmon Subrayamos el carácter « funcional » de esta rigidez reversible por aerosoles adrenalina eufilina etc o de modo espontáneo al cesar la crisis que no puede evocar en ningun caso una resultante de alteraciones orgánicas anatomopatológicas Esta rigidez o sea descenso de compliance » en su aspecto funcional deriva de la menor distensibilidad propia así como del aumento de viscosidad y de las resistencias bronquiales Podemos llamarla compliance funcional frente a la compliance estatica que deriva solamente de la reaccion elastica del pulmon En el sujeto normal ambas compliance estática u funcional son prácticamente iguales pues la resistencia bronquial

es puramente lineal derivada de la viscosidad del gas según el análisis hecho por Otis y cols es proporcional a la velocidad de paso frente a la que llaman resistencia turbulenta » proporcional a la vel ² que se establece cuando cambian las condiciones del flujo oponiendo entonces una resistencia mucho mayor En el sujeto normal las cualidades de los bronquios son tales que evitan la turbulencia del flujo Ya en el sujeto normal según Dayman existe en una pequeña proporción colapso espiratorio de los bronquiolos que produce un aumento de resistencia al final de la espiración Pero en tanto que en el normal las compliance estática y funcional difieren poco son muy distintas en el enfisematoso o en la crisis asmática así se ve la presión intraesofágica aumentarse en la espiración hasta valores positivos La compliance estática puede ser normal en el asma o estar aumentada (Chermack) pero la funcional aparece muy disminuida Tal disminución deriva esencialmente del aumento de resistencia bronquial lo cual es natural además de confirmarse por el empleo de aerosoles broncodilatadores en la crisis (Chermack Sherrer y cols) Tal aumento en gran parte derivado del estrechamiento actual del calibre bronquial (secreción edema espasmo) corresponde como luego veremos al colapso espiratorio de los bronquiolos no cartilaginosos que actuan como válvula de control check valve mechanism según la expresión de Ch Jackson ya entrevista por Biermer y cuya importancia ha sido subrayada por Dayman La inhomogeneidad de la mezcla, el colapso bronquial explican que a medida que aumenta la frecuencia respiratoria se aumentan las resistencias y es mayor la rigidez o menor la distensibilidad pulmonar durante el ciclo (Otis Mc Kerror etc Attinger y cols Chermack Scherrer y cols) La llamada constante tiempo t resulta del producto Compl × resist = T Es fácilmente comprensible que la velocidad del flujo debe derivar de la reaccion elástica y de la resistencia opuesta

En el *aumento de la resistencia del flujo* juegan como hemos dicho esos dos factores viscancia tisular y restricción bronquial siendo en la crisis asmática difícil de estimar cada uno con seguridad Diferentes métodos pueden dar valores no coincidentes su estimación más segura puede hacerse sin duda con la metódica empleada por Comroe Du Bois y cols Evidentemente lo más importante es el aumento de la resistencia restictriva bronquial Hablamos de restricción de modo genérico para no prejuzgar sobre su mecanismo espasmo edema secreción u oclusión Por uno u otro mecanismo la obstrucción bronquial mas o menos intensa y difusa produciendo una mayor resistencia al paso del aire en ambas direcciones es sin duda un factor de decisiva importancia en la crisis asmática Por otra parte el aumento de presión pulmonar espiratoria que se hace superior en la espiración forzada a la tensión del tejido y por consiguiente a la presión luminar en los bronquios permite que estos se colapsen haciendo su aparición ese mecanismo de « check valve » que anula la espiración aumentando el « trapping » del aire Este factor se añade con mayor intensidad a los otros de restricción bronquial en la espiracion forzada y rápida También la viscancia aumenta hasta más de 5 veces siendo en la espiración mayor que en la inspiración cuando es en cambio igual en ambas fases de la respiración normal El trabajo respiratorio como puede medirse por integración gráfica sobre los datos anteriores aparece notablemente aumentado hasta más de 8 10 veces lo normal Este aumento es un factor en la retención de carbónico que se

suma a la anoxia constituyendo el cuadro de la « insuficiencia global » segun Rossier Scherrer y cols tambien se suman a este punto de vista El trab jo respiratorio puede ser mayor de lo que traduce la medida de las resistencias elástica viscosa y bronquial V Wyss y cols han apoyado su tesis de la rigidez de los musculos inspiratorios entre otros argumentos en el hallazgo de casos con flujo disminuido sin aumento de la presión intraalveolar

La *ventilacion de la sangre* en la reacción asmatica puede ser normal como ya demostramos hace muchos años con el estudio de gases en sangre arterial y venosa incluso en la crisis Sin embargo en un cierto numero de casos se encuentra disminuida la saturación por O_2 de la hemoglobina asociada a disminución del $PaCO_2$

Segun la época en que se han ido haciendo nuestras determinaciones hemos utilizado la punción radial o femoral y hecho los analisis en el aparato de Haldane en el v Slyke o con el oximetro El cálculo de PCO_2A se ha hecho por el método indirecto de Rahn y Otis aplicando la formula que deriva de la ecuación del aire alveolar I I PaO_2 y PaCO por el método de Riley y Proemmel de la burbuja

La inhomogeneidad de distribución del aire que supone la existencia de zonas mejor y otras peor ventiladas es la causa principal del cuadro de hipoxia hipocapnia En algunos asmáticos crónicos puede verse persistir la hipooxia en los intervalos cuando existe un enfisema con adaptación del sujeto a saturaciones más bajas La *mezcla venosa* por la sangre de zonas menos ventiladas estimada por la respiración a dos niveles de oxígeno segun Riley y Cournand alcanza hasta el 40 p 100 en tanto que es de 7 p 100 en el normal Con el mismo metodo hemos podido ver que no hay un transtorno de difusión de membrana aunque el gradiente A a esté elevado Se eleva en el enfisema y por consiguiente puede haber un efectivo transtorno de difusión en asmáticos con hipooxia pero es en el asma crónico complicado con disminución del lecho capilar Rossier y cols (Lunchsinger etc) sugieren que la disminución de capilares puede conducir a una falta de circulación colateral lo cual originaría para el mismo volumen de expulsión cardíaco un aumento de velocidad de paso de la sangre con lo cual el factor tiempo de contacto de evidente importancia sobre todo cuando el PAO_2 sea bajo (Bartel) se reduce y ello puede originar una menor oxigenación de la sangre

En lo referente a *la circulacion pulmonar* la crisis de asma no modifica en nuestra experiencia el índice cardíaco Otros AA (Wstcott y cols Sherrer y cols) han hallado lo mismo La presión en la arteria pulmonar no se modifica tampoco salvo en crisis con cianosis e hipercapnia o en enfermos con asma inveterado al que se asocia enfisema y acidosis respiratoria En estos casos la presion capilar medida como « wedge pressure » se conserva normal y el gradiente art pulm—capilar se eleva A partir de las observaciones experimentales de v Euler y Lijilstrand se ha interpretado esta hipertensión pulmonar como consecuencia de la anoxia sin duda en el gato la anoxia eleva la presión pulmonar aun en segmentos de pulmón aislado y en animal anestesiado (Duke Hall) Aviado y cols en el perro no confirmaron ese efecto el resultado es variable por existir varios factores en juego segun estos AA la anoxia originaria vasodilatación pulmonar tendiendo a elevar la presión un reflejo por estímulo de los quimioceptores sinocarotídeos y por liberación de adrenalina El estímulo eléctrico del seno produce descenso

de la presión pulmonar y la oclusion de las carotidas la eleva aun después de extirpado el estrell do y en animales suprarren lectomizados (Burgh Daly) lo que indicaría que no se debe a cambio de calibre vascular En el asma el aumento de la presion intraalveolar puede ser un factor de aumento de resistencia capilar experimentalmente por respiración a hiperpresión nosotros hemos visto elevarse la presión en la arteria pulmonar en el perro y en enfermos asmáticos Una relación más estrecha que con la anoxia hemos h llado nosotros así como también Yu y cols Harvey y cols Scherrer y cols con el grado de hipercapnia Es muy verosímil que el defecto de ventilación de l sangre determine la liberación de alguna substancia hiper tensora Daly ha visto que l s anticolinesterasas aumentan la presión art pulmonar Cournand y cols por su parte han visto que la inyección de acetilcolina eleva la presión ya aumentada por la anoxia Nosotros hemos pensado que l serotonina con la que puede provocarse hipertensión pulmo nar y broncoconstricción podría jugar un papel en el asma y en el enfisema en la dinámica de las crisis y en la hipertensión pulmonar Sin embargo no hemos podido hallar modific ciones sensibles en el contenido de serotonina en la sangre arterial venosa y del círculo menor tampoco hemos hallado aumento de la eliminación de indolacético en la orina en estos enfermos

Si queremos ahora hacer una *definicion sintética de la reaccion asmatica* desde el punto de vista neumodinámico diríamos que es una situación reversible caracterizada por la insuflacion con rigidez funcional del pulmón cuyos principales caracteres son la elevación de la posición media el aumento del aire residual y el espacio muerto funcional una dificultad limitada en la velocidad inspiratoria y una dificultad fundamental en la espiración principalmente debida a un aumento de la resistencia en parte por aumento de viscancia pero sobre todo por la obstrucción bronquial que se acentu en la espiración forzada por el colapso de los bronquiolos Todo ello determina el descenso actual de la el sticidad disminución de la compliance y oscilaciones amplias de la presión intr toracica que traspasan el limite de la disnea así como inhomogeneidad de distribución del aire con zonas menos aireadas y aumento de la mezcla venosa La repercusión sobre la ventilacion de la sangre depende del grado de dificultad a la ventilación de esta inhomogeneidad y del grado de aumento del trabajo respiratorio La repercusion sobre la presion pulmonar tiene alguna relacion con el aumento de presion intraalveolar y con la mala ventilación de la sangre interviniendo algunos otros mecanismos no aclarados

II MECANISMO EN EL ASMA BRONQUIAL DE LA REACCIÓN ASMÁTICA

Seguramente no es uno solo el mecanismo determinante de los fenómenos que hemos visto que caracterizan a la R A En las crisis varios de ellos se imbrican y segun el predominio en cada caso de unos y otros el tipo clínico y el caracter mas breve o prolongado cambian La tesis del *broncospasmo* ha gozado de un favor preferentemente sin duda hay aparte de las razones experimentales (estimulo de vago choque anafiláctico del cobaya) razones clinicas (presentación brusca en las crisis mas agudas) y farmacologicas

(efectos de la adrenalina atropina y aerosoles broncodilatadores) en favor de la realidad de un espasmo bronquial A ellas hay que añadir la observación broncoscópica de Pasteur Vallery Radot y cols La disposición de la musculatura bronquial estudiada de nuevo en los ultimos años por Miller Policard Batilsberger y otros permitiría aceptar una acción de esfinter en las dicotomías Sabemos que se extiende hasta los ducti y de aquí sobre los sáculos se apoya en el origen de los alveolos Actualmente parece verosimil que los alveolos no aumenten sino acaso disminuyan (Dayman) de tamaño durante la inspiración en la cual « la forma de taza se cambia en forma de salsera » Por otra parte existe una musculatura intersticial estudiada de nuevo por Niedner que se ve hipertrófica en enfermos respiratorios crónicos (cirrosis pulmonar muscular (Buhl etc)) Sturm ha dado argumentos en favor de la naturaleza contractil del órgano pulmonar Nosotros hemos discutido posibles funciones fisiológicas todavía desconocidas de este complejo sistema muscular que evidentemente debe tener Un cierto tono de la misma contribuiría a mantener patentes los alveolos y bronquiolos siendo en este sentido un auxiliar de la inspiración como ha sugerido A O M Wyss Es verosimil que pueda favorecer la difusión del oxígeno aumentando electivamente la presión intraalveolar El efecto broncodilatador de la adrenalina sobre el preparado bronquial contraído por la histamina ha sido demostrado por nosotros pero no puede olvidarse que la acción de la adrenalina es más compleja y también hace su efecto en la urticaria y en el edema angioneurótico independientemente de toda acción muscular En cuanto a la pituitrina que puede cortar tambien la crisis se revela en el preparado como constrictora y la eufilina no tiene acción sobre el musculo bronquial en nuestras experiencias

Todo indica que al lado del posible broncospasmo verosímil pero sobre el que como dicen Lowell Meyer y Rappaport etc no tenemos evidencia actual hay otros fatores de importencia decisiva Nosotros hemos tenido ocasión de hacer dos autopsias de enfermos muertos en acceso de asma muy precozmente y publicado nuestras observaciones Lo que es mas impresionante es la *obstrucción de bronquios gruesos* y medianos *por moco* y la *enorme actividad secretora* de las glandulas anejas que aparecen distendidas y repletas Esta violenta hipercrinia vista por Huber y Koessler ha sido tambien senalada por Letterer Riva y Probst y otros Además de esta hipersecrecion obstruyente contribuye el edema de la mucosa a veces intensísimo hace unos anos hicimos realizar en nuestro servicio numerosas observaciones broncoscópicas en la crisis de asma tambien han sido hechas por otros muchos AA (P Vallery Radot y cols Soulas y Mounier Kuhn Fruchtman Wyss etc) En algunas ocasiones predominan el enrojecimiento y el edema terso recordando el edema angioneurótico o la urticaria con mucosa más bien seca y mate Otras veces se aprecia sobre todo la gran hipersecreción y la obstruccion por ella En algunos casos hemos visto un fenómeno también descrito por otros la protrusión de la mucosa en la espiración incluso en los tramos altos Tambien puede verse el colapso bronquial de la espiracion forzada Todos estos factores contribuyen al aumento restrictivo de la resistencia bronquial aunque a ellos se sume el broncospasmo este no puede ser directamente visto como lo son estos otros factores Aschoff él mismo asmático propuso distinguir dos tipos de crisis una de comienzo brusco violenta que sería principalmente espás

tica, y otra de instauración más lenta menos sofocante y de mayor duración en la que jugaran otros mecanismos. No obstante como nosotros vimos al segundo enfermo autopsiado empezar de la primera forma y morir rápidamente y en la autopsia descubrimos la hipercrinia y la obstrucción por secrecciones creemos que este puede ser también el factor principal aun en las crisis bruscas. La contracción de la traquea ha sido incriminada por Groen y cols.

No puede no obstante lo anterior negarse la intervención de más factores. Nosotros creemos que un factor importante es la *plenificacion del circulo menor* en el sentido sugerido por Grosmann y v. Basch. Poniendo en comunicación con la tráquea un balón inflado se ve cómo pierde aire por pasar a la tráquea cuando se aumenta la plenificación del sistema pulmonar. Nuestras experiencias con un preparado pulmonar encerrados los pulmones en una cámara sometida a cambios rítmicos de presion como en la respiración normal demuestran que si se aumenta la plenitud del círculo menor por estrechamiento de las venas pulmonares el pulmón se ingurgita, tomando más aire y su curva respiratoria se hace similar a la de la crisis de asma. Tsuji y cols. sugieren la contracción sinérgica de los musculos bronquiales y de las venas pulmonares. Estudiando el contenido de sangre en el sistema pulmonar y la sangre total circulante en el cobaya y sus modificaciones a diferentes tiempos de provocación del choque anafiláctico pudimos demostrar el desplazamiento de sangre al círculo menor realizada agudamente. En experiencias posteriores con pinzamiento parcial de la tráquea tambien pudimos ver que éste origina una ingurgitación sanguínea del circulo pulmonar: parece que se trata de una reaccion coordinada a la respiración en estenosis. En la R. A. que se presenta en enfermos con estenosis mitral o en hipertensos podría esta ingurgitación eréctil del pulmon ser el mecanismo fundamental en juego; no obstante Saxton y cols. no han visto variar la compliance por el aumento de presión venosa. Borst y cols. han visto en cambio un descenso de compliance cuando se produce una hipertensión en la auricula izquierda, aunque no sea aquella tan intensa como podría corresponder a la hipertensión venosa creada.

Wintrich sugirió la hipótesis de un *calambre del diafragma* como mecanismo de la R.A. basándose en razones puras de observacion clínica. Esta hipotesis ha estado olvidada por la creencia generalizada en el broncospasmo como mecanismo fundamental. Es indudable que el espasmo del diafragma no podría explicar univocamente la crisis, pero otra cosa es negar su existencia y restarle un valor cooperativo en su produccion. Nosotros defendimos su realidad hace varios anos: la radioscopia del enfermo en crisis de asma demuestra la posicion baja del diafragma y su inmovilidad en el ciclo respiratoria; no se trata de una atonía que por el contrario le colocaría en posicion mas alta y determinaria un movimiento paradojico; tampoco creemos que es un fenomeno pasivo de empuje por el pulmón dilatado porque hemos visto recuperarse su movilidad fuera de las crisis independientemente de la persistencia de la insuflación. V. Wyss y cols. dieron argumentos deducidos del estudio paralelo de la presión alveolar y neumotacograma. Evidentemente otros factores tienen una importancia mayor a nuestro juicio en la produccion de la crisis, pero esto no excluye la cooperacion de la rigidez muscular inspiratoria.

En el aumento de la viscancia debe intervenir el *edema intersticial* del

pulmón del cual hemos aportado pruebas histológicas y químicas por análisis del contenido en agua del pulmón. Halpern y cols han corroborado este edema al cual otorgan tambien importancia en la dinámica de la R A

Cuando sepamos mejor cómo actuan los fármacos que frenan ó suprimen la crisis de asma esto contribuirá sin duda a valorar los más importantes entre los factores analizados Nosotros hemos visto cómo el efecto de los esteroides puede verse como en este caso de nuestra observación que ponemos como ejemplo sin que se modifique la V C y la M B C sobre la circulación pulmonar y los gases de la sangre La eufilina actua sobre el trabajo cardíaco presión en la pulmonar y volumen de expulsion en estudios hemodinámicos realizados por nosotros en sujetos con R A La adrenalina que podrá ser effectiva en parte contra el broncospasmo tiene otras acciones antiedema antisecretora y segun Borst y cols vasodilatadora Binet y cols han señalado cómo después de la adrenalina disminuye el contenido en sangre del círculo menor El descenso de las resistencias y el aumento de compliance producidos por estos fármacos se hace sin duda actuando bajo aspectos distintos que deben ser considerados como parte de un conjunto complejo de secuencia de hechos coordinados En la R A provocada por un choque alérgico parece natural admitir como factores primarios la hiper secreción el espasmo bronquial la ingurgitacion vascular en los pulmones y el edema intersticial Nosotros hemos visto en un enfermo que murio en crisis violenta de asma también en el hígado un edema disociante con zonas de congestión y de isquemia hipersecreción de moco en los conductos biliares y obstrucción de algunos de ellos por secreción y células descamadas Riva y Probst también han observado discrinia pancreática en la crisis Todo ello contribuye a aceptar que en el choque alérgico que provoca la crisis asmática convergen varios factores que aunque tienen su máxima expresión en el pulmón también se proyectan sobre otros órganos

Qué mecanismos son preponderantes en la produccion de la R A en otras formas etiológicas cuerpo extraño traumas cancer bronquial bronqueicta sias etc no nos es posible analizarlo Un interés especial ofrece a la investi gacion futura el modo de acción provocadora de influencias no alergénicas en los asmáticos por ejemplo cambios en la polución del aire atmósferas confinadas humedad y otras alteraciones metereológicas Nuestro colabora dor Alcalá trabajando con Du Bois y el grupo de Comroe ha visto cómo la respiración de un aire conteniendo tinta china provoca una r asmática con aumento de la resistencia bronquial al flujo del trabajo respiratorio y leve descenso de la compliance En el estudio broncoscópico y broncográfico de asmáticos primarios se pueden encontrar afecciones parietales deformantes o estenosantes que originan una R A aparentemente primaria (Massman Osmind Mead y cols Waldbott Derbes y cols etc)

III. FACTORES Y MECANISMOS DE COMPLICACIÓN EN LA EVOLUCIÓN ULTERIOR DEL ASMA

Con frecuencia a medida que evoluciona el asma pierden violencia las crisis al tiempo que los intervalos van siendo menos libres hasta llegar a convertirse en un cuadro permanente con acentuaciones intermitentes en relación con infecciones eventuales, influencias psíquicas, factores atmosféricos u otros influjos funcionales (menstruación, menopausia, etc.). Entonces se habla del asma inveterado. La intervención puede ser la consecuencia de haberse ido haciendo lesiones orgánicas a fuerza de repetirse el stress que supone la crisis funcional. Son, en esquema, las principales vías de esa transformación: la enfermedad orgánica respiratoria, el desequilibrio iónico, principalmente acidosis, hipoxia, hipercapnia, la asistolia derecha y la aparición de procesos sumados de gran difusión en el organismo, afectando principalemente los vasos y tejido conectivo.

Con respecto a lo primero, lo más frecuente e importante es *la evolución al enfisema*: el enfisema broncógeno u obstructivo es con gran frecuencia la consecuencia del asma. No es obligado que esta evolución suponga una alteración estructural. Loechske insistió sobre la naturaleza puramente funcional del enfisema broncógeno, que desde el punto de vista anatomopatológico no puede considerarse como auténtico aunque lo sea para el clínico. Nosotros subrayamos hace muchos años esta disociación entre el enfisema en la mesa de autopsias y el enfisema en la clínica, y analizamos los factores neumodinámicos diferencialmente en el enfisema estructural involutivo o toracógeno y el enfisema broncógeno. Por otra parte, hemos tenido ocasión reiterada de ver asmáticos con sintomatología continua de enfisema en los que los síntomas han revertido totalmente con motivo de una ictericia, una nefropatía albuminúrica o un mixedema. Esta sorprendente desaparición momentánea del enfisema obstructivo se puede ver actualmente con gran frecuencia por el tratamiento con ACTH y esteroides. No obstante, a la larga se puede hacer el enfisema estructural, sobre todo ocurre esto en los niños con asma subintrante, y colabora seguramente la deformación que secundariamente se fija del tórax. También deben señalarse la bronquitis y bronquiectasias, cuyo mecanismo es similar al de las sinusitis: infección de una mucosa alérgica tumefacta, edematosa, por gérmenes de invasión secundaria. Esta patología secundaria de los bronquios tiene una gran importancia en la evolución del asma: se pueden producir subobstrucciones que, favorecidas por la afección parietal, originen las bronquiectasias, muy frecuentes si se buscan intencionadamente (Overholt y cols., Prickman y Moersch, etc.).

Con respecto al segundo punto, es necesario tener presente cómo en el asma en su evolución crónica se puede producir la *acidosis respiratoria* como aparece en el enfisema, o en las fibrosis. Muchos asmáticos se adaptan a la hipoxia, que toleran perfectamente: vemos con relativa frecuencia asmáticos con saturaciones inferiores a 80 p. 100 y sin disnea en reposo, sin cianosis, con ligera poliglobulia o sin ella, con aumento del valor hematocrítico (aumento del volumen globular) (v. también Wilson y cols.). Trabajando hace muchos años con mi maestro Adolfo Leeroy pudimos

observar como los enfermos cianoticos eran menos sensibles a la respiración con un aire de mayor contenido en CO_2 hecho que actualmente está bien comprobado La insensibilidad del centro respiratorio al carbónico está apoyada por el aumento de la reserva alcalina (Fishman y cols) En esta situación de hipercapnia acidosis la regulación respiratoria se hace princi palmente por el estímulo sobre los quimioceptores de la hipooxia La corrección del desequilibrio iónico que la respiración supone normalmente a cargo del centro respiratorio se hace aqu defectuosamente y se origina un cuadro sui generis de cefalea y trastornos psíquicos que puede incluso imitar un tumor cerebral tendencia al coma y coma confirmado al final cianosis edemas oliguria etc Muchos casos en esta situación son con siderados y tratados erróneamente como en hiposistolia sobre todo por la oliguria y los edemas Nosotros hemos descrito este cuadro de « pseudoasis tolia » en el asma y enfisema en el que la ausencia de disnea la preferencia por el decubito la bradicardia y la ausencia de estasis hepático permiten hacer una diferenciación fácil La oliguria y los edemas tienen una causa no bien conocida posiblemente como han sugerido Brod y cols y Stuart Harris y cols la situacion ionica suscita la liberación al círculo de alguna substancia adrenérgica responsable de esa parte del cuadro

La *hiposistolia derecha* es otro de los caminos enunciados En el asma transformado en una enfermedad orgánica respirato ia la hipertensión pulmonar es el mecanismo de la hiposistolia derecha ulterior Sin embargo debe subrayarse que el asma en si produce con sorprendente rareza hiposis tolia incluso en enfermos con grandes crisis no se ve repercusión cardiaca y tanto el volumen radiologico del pulmón como en el análisis hemodinámico el índice cardiaco no experimentan modificaciones En el asma grave con cianosis e hipercapnia la presión en la arteria pulmonar puede elevarse transitoriamente Es verosímil que influya también la producción de los shunt de arterias bronquiales a vasos pulmonares ya senalados por Eppinger en el siglo pasado y que segun la expresión de Giese viene a constituir una « aortizacion » del círculo pulmonar Sin duda un factor fundamental es la reducción progresiva del lecho capilar

En el asma por ultimo aparece en ocasiones sucediendo a esas dos fases anteriores funcional y pática una fase que hemos descrito como « *angiome senquimal* o angioconectiva en la cual aparecen lo variados cuadros clinicos que pueden verse en las llamadas enfermedades del colágeno Mencionemos simplemente los cuadros de infiltrado agudo maligno del pulmon con fiebre alta y gran repercusión general (Rackemann Harkavy nosotros Turiaf y cols) que tendrían la significación segun Harkavy de alergia vascular la asociacion de cuadros reumáticos y de manifestaciones cutáneas similares a las de las angitis alérgicas la asociacion con la periartritis nudosa que no es excepcional la evolucion de algunos casos con un cuadro maligno y forma ción de granulomas (granulomatosis patergicas) la nefritis intersticial con repercusion sobre la funcion renal etc La etiologia de estos procesos es muy obscura y sabemos que tienen que ver con el mecanismo alergico pudiendose en ocasiones descubrir la influencia de una alergia a drogas o infecciosa Esto hace verosimil que mas bien que una complicacion del asma se trate del despleganmiento ulterior de un proceso que se inicio como asma como otras veces puede iniciarse por urticaria o edema de Quincke Favorece este punto de vista el hecho de que la mayor parte de estos casos habian

ofrecido ya una evolución maligna subintrante del asma frente a los numerosos casos de asma crónico que no presentan nunca esta transformación

En los trabajos de nuestro conjunto sobre los que basamos nuestros puntos de vista colaboraron en épocas sucesivas de modo fundamental los Dres Sánchez Cuenca Centenera Agesta Quintero Alemany Arjona Alés López García Grande Cobián de Oya Morales Perianes y últimamente continuan sus investigaciones en el departamento especial de nuestro Instituto los Dres F Lahoz R Alcalá P de Rábago F Sastre Pérez Guerrero Sokolowsky y Marín A todos ellos deseo expresar mi gratitud por su valiosa cooperación

RESUMEN

Se describe la reacción asmática (R A) como una alteración de la dinámica respiratoria con ciertos caracteres típicos entre los que resaltan la insuflación con cierta rigidez funcional del pulmón dificultad principalmente espiratoria secuestro de aire e inhomogeneidad del reparto del aire inspirado Se hace el análisis neumodinámico de la R A concluyendose en la importancia fundamental del aumento de resistencias por aumento en parte de la viscosidad de tejido pero muy principalmente de la resistencia bronquial El conjunto resulta de una serie de mecanismos entre los que se analizan el espasmo bronquial (la hipersecreción la obstruccion el edema y el colapso de los bronquiolos en la espiración forzada colaboran en la crisis la ingurgitación del círculo menor y la rigidez de los musculos inspiratorios La R A puede ser primaria como en el asma bronquial o implantarse como reacción secundaria en enfermedades respiratorias o circulatorias diversas Los factores que juegan el papel principal se combinan diferentemente en cada tipo etiológico aunque el resultado dinámico sea equivalente La repercusión sobre el cambio de gases con la sangre es distinta segun el tipo de la crisis y su período evolutivo desde no afectarse a producirse la anoxia con hiperventilación carbónica o sumarse la anoxia e hipercapnia La anoxia con hiperventilación deriva de la inhomogeneidad del reparto coexistiendo zonas bien ventiladas y zonas mal ventiladas (aumento de la mezcla venosa) tambien puede resultar de la obstrucción que obstaculiza más difusamente la ventilacion en cuyo caso el carbónico puede estar aumentado El aumento de trabajo respiratorio es un factor en la retención de carbonico y aumento de la anoxia

Se estudian los mecanismos de inveteración del asma la enfermedad funcional puede irse haciendo cada vez más orgánica a traves de la reiteración de las crisis y la infeccion el enfisema estructural y las broncopatías son sus principales secuelas La mala oxigenacion de la sangre y la acidosis por retención de carbónico irrogan una serie de alteraciones secundarias que son analizadas La disminución del lecho capilar la hipercapnia y acaso la creación de shunts participan en la produccion de la hipertension del círculo menor que puede en los casos inveterados conducir a la asistolia derecha Otros sintomas generales en el asma inveterado tienen su raiz en la misma disreacción alergica

RÉSUMÉ

L auteur decrit la dyspnée asthmatique comme etant un trouble de la dynamique respiratoire avec certains caracteres typiques distension pulmonaire accompagnee d une certaine rigidité fonctionnelle difficulte surtout expiratoire ventilation insuffisante distribution non homogene de l air inspiré

L auteur fait l analyse de la dynamique de la dyspnee asthmatique et il conclut à l importance fondamentale de l augmentation des resistances due à la viscosité des tissus et aussi à la resistance bronchiolaire L auteur analyse l ensemble des mecanismes qui provoquent la dyspnee asthmatique notamment le spasme bronchique l hypersécretion l obstruction l œdeme et le collapsus des bronchioles pendant l expiration forcée A ces troubles s ajoutent la surcharge de la petite circulation et la rigidite des muscles inspiratoires La dyspnee athmatique peut etre *le phénomene principal* comme dans l asthme bronchique ou constituer une *réaction secondaire* dans diverses maladies respiratoires ou circulatoires

Les principaux facteurs se combinant differemment suivant le type etiologique bien que le resultat dynamique soit le meme l influence sur l echange gazeux sanguin est differente selon le type de la crise et sa periode evolutive

Parfois il n y a pas d effet parfois il se produit une anoxie avec hyper ventilation carbonique ou bien une anoxie avec hypercapnie L anoxie avec hyperventilation decoule de la non homogeneite de la distribution de l air inspire du fait qu il y a des regions plus ou moins ventilées (augmentation du melange veineux) elle peut aussi resulter de la diminution de la ventilation Dans ce cas la quantité de gaz carbonique peut etre augmentee L accroissement du travail respiratoire est un des facteurs de la retention de gaz carbonique et de l accroissement de l anoxie

L auteur etudie les mecanismes qui aboutissent à l asthme invetere la maladie fonctionnelle se transforme lentement en un etat organique par suite de la répetition des crises et des infections l emphyseme structural et les bronchopathies en sont les sequelles principales L oxygenation insuffisante du sang et l acidose par rétention de gaz carbonique produisent une serie de troubles secondaires qui sont analysés La diminution du lit capillaire l hypercapnie et peut etre la formation de shunts participent à *l hypertension dans la petite circulation qui peut dans les cas d asthme* invétere conduire a l asystolie droite Il existe d autres symptomes généraux ayant leurs origines dans les memes troubles allergiques

SUMMARY

The author describes the asthmatic dyspnea as being a disturbance of the pulmonary dynamics with certain typical characters pulmonary distension accompanied by functionnal rigidity essentially expiratory difficulty insufficient ventilation and non homogenous distribution of the inspired air

The author analyses the dynamics of the asthmatic dyspnea and empha

sizes the fundamental importance of the increased tissular resistance due to the augmentation of their viscosity and also of the resistance in the bronchial tree. He studies the general mechanisms which lead to the asthmatic dyspnea and particularly the bronchial spasm, the hypersecretion, the obstruction, oedema and the bronchial collapse during the forced expiration. To all these disturbances one should add the overload of the small circulation and the rigidity of the inspiratory muscles. The asthmatic dyspnea may constitute the principle phenomenon as it is in asthma or may be a secondary reaction in various circulatory or respiratory diseases.

The various main factors may intervene differently according to the etiological type although the dynamic ventilatory results may be the same. The effect of the blood gazeous exchanges is different according to the type of the attacks and the evolution. Sometimes there is no effect; often anoxia and carbonic hyperventilation occurs, but also sometimes anoxia with hyper capnia. Anoxia with hyperventilation result of non homogenous distribution of the inspired air (increase of the veinous mixing) but it can also be the consequence of the decreased ventilation. In the latter case the quantity of carbondioxyde is increased. The augmentation of respiratory work is one of the factors which leads to the retention of carbondioxyde and determines the aggravation of the anoxia.

The mechanisms which lead to the intractable asthma are analysed: the primarely functionnal disease changes progressively into an organic state as a consequence of the repetition of attacks and infections, organized emphysema and bronchopathies are the main sequellae. The insufficient oxygenation of the blood and the acidosis by carbondioxyde retention cause a series of secondary troubles which are studied. The reduction of the capillary bed, the hypercapnia and also the establishement of circulatory shunts are involved in the pulmonary hypertension in intractable asthma and lead to the right asystolia. There are many other general symptoms which originate from the same main allergic disturbances.

ZUSAMMENFASSUNG

Der Autor beschreibt die asthmatische Dyspnoe als Störung der Atmungsdynamik mit gwissen typischen Kennzeichen: mit einer gewissen Funktions rigidität begleitete Lungenerweiterung, besonders Exspirationsschwierigkeit, ungenügende Durchlüftung, ungleichmässige Verteilung der eingeatmeten Luft.

Der Autor analysiert die Dynamik der asthmatischen Dyspnoe und er schliesst auf eine fundamentale Bedeutung der Zunahme der Widerstände bedingt durch die Viskosität der Gewebe und besonders durch den bronchiolaren Widerstand. Der Autor analysiert die Gesamtheit der Mechanismen, die die asthmatische Dyspnoe bewirken, namentlich den Bronchospasmus, die Hypersekretion, die Obstruktion, das Ödem und den Bronchiolenkollaps während der forcierten Ausatmung. Diesen Störungen fügen sich eine Ueberbelastung des kleinene Kreislaufes und eine Rigidität der Inspirationsmuskeln hinzu. Die asthmatische Dyspnoe kann das hauptsächlichste Phänomen beim Bronchialasthma sein oder als Sekundarreaktion bei verschiedenen Atmungs- und Kreislaufkrankheiten auftreten.

Den hauptsachlichen Faktoren verbinden sich je nach dem Atiologietyp in verschiedener Weise obgleich das dynamische Resultat dasselbe ist ist der Einfluss auf den Gasaustausch des Blutes je nach der Anfallsart und der Entwicklungsperiode verschieden

Manchmal sieht man keine Wirkungen manchmal entwickelt sich eine Anoxie mit einer Kohlensaurehyperventilation oder eine Anoxie mit einer Hyperkapnie Die Hyperventilationsanoxie beruht auf der un gleichmassigen Verteilung der eingeatmeten Luft so dass es besser und schlechter durchluftete Regionen gibt (Vermehrung des Venegemisches) sie kann aber auch auf einer Ventilationsverminderung beruhen In diesem Fall kann die Kohlensauremenge vermehrt seib Die Zunahme der Atem tatigkeit ist einer der Faktoren bei Kohlensaureretention und Anoxie zunahme

Der Autor studiert die Mechanismen die zu einem veralterten Asthma fuhren die funktionalle Krankheit wandelt sich langsam in einen orga nischen Zustand um bedingt durch die Wiederholung der Anfalle und Infektionen das strukturelle Emphysem und Bronchopathien sind die hauptsachlichen Krankheitsfolgen dabei Die unzureichende Sauerstoff beladung des Blutes und die Azidose durch Kohlensaureretention be [illegible] nalysiert werden Die Verk [illegible] und vielleicht die Bildung [illegible] am Hochdruck im kleinen Kreislauf der in Fallen mit einem veralterten Asthma zu einer Rechts herzinsuffizienz fuhren kann Es gibt noch andere allgemeine Symptome die ihren Ursprung in den gleichen allergischen Storungen haben

ÉTUDE DE LA FONCTION RESPIRATOIRE DANS L'ASTHME ET DANS L'EMPHYSÈME

par

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Les troubles de ventilation au cours de l'asthme et de l'emphysème obstructif sont bien connus actuellement. Nous savons qu'une crise d'asthme peut s'accompagner d'une hyperventilation globale, d'une insuffisance de distribution nommée aussi insuffisance partielle ou d'une hypoventilation alvéolaire (insuffisance globale).

En unissant spirométrie et analyses du sang artériel on peut étudier sans peine les dysfonctions ventilatoires de l'asthmatique ou de l'emphysémateux. Ceci est à la portée de tout laboratoire bien équipé.

Les réactions du cœur droit au cours de l'asthme sont également bien connues aujourd'hui grâce entre autres aux travaux de Scherrer et coll. (1956). On sait qu'une hypertension dans la petite circulation n'apparaît lors de la crise d'asthme qu'en cas d'hypoventilation alvéolaire conformément aux conceptions modernes de physiopathologie cardio-pulmonaire (voir Rossier et Bühlmann, 1954). Si la crise d'asthme ne provoque qu'une inégalité de répartition de l'air inspiratoire (insuffisance de distribution ou insuffisance partielle), il n'y a pas de surcharge fonctionnelle du cœur droit, une défaillance de cet organe n'est pas à craindre.

Si ces problèmes ont été bien étudiés, il n'en reste pas moins vrai que la mécanique respiratoire au cours de l'asthme et de certaines formes d'emphysème obstructif fait encore l'objet de discussions. Or, nous croyons pouvoir dire que le problème de la mécanique respiratoire lors de la crise d'asthme est en fait résolu dans ses grandes lignes, mais cela nécessite une revision des conceptions classiques concernant les notions fondamentales de la mécanique respiratoire.

Ce qui caractérise l'asthme et l'ensemble des affections asthmatiques, c'est l'apparition de sténoses au niveau des bronches et surtout des petites bronches et bronchioles. Je m'excuse d'insister sur un fait aussi bien connu, mais comme on le verra il a des conséquences inattendues.

Analysons les éléments principaux de la mécanique pulmonaire classique. Si l'on considère le poumon en laissant de côté toute la question du thorax

on se rend compte qu'il est possible d'analyser la dynamique pulmonaire grâce à des enregistrements de pression pleurale ou œsophagienne unis à des tracés spirométriques ou pneumo-tachographiques.

Lors de l'inspiration, les muscles respiratoires travaillent contre deux sortes de résistance, l'expiration étant à l'état physiologique un acte purement passif. En effet, les muscles inspiratoires doivent surmonter tout d'abord les résistances dues aux forces de rétraction du poumon. Si l'on mesure la pression pleurale ou œsophagienne correspondant à deux états de distension du poumon, on peut calculer le coefficient d'élasticité. Ce coefficient a été nommé « élastance » par Bayliss et Robertson (1939); on utilise aussi sa valeur réciproque que Mead et coll. ont nommé « compliance ». Il faut en moyenne une force de 4 à 10 cm d'eau pour vaincre les résistances élastiques lors d'une distension pulmonaire correspondant à un litre d'air. Les forces nécessaires pour surmonter les résistances élastiques représentent une fonction linéaire par rapport aux variations de volume, et cela à l'état physiologique.

Mais lors de l'inspiration, les muscles doivent vaincre encore d'autres résistances et principalement celles apparaissant dans les canaux bronchiques lors du passage de l'air, ces résistances étant une fonction de l'intensité du flux aérien et non du degré de distension du poumon. Ce sont surtout les déplacements laminaires de l'air qui sont importants, les résistances dues à la turbulence ne jouant à l'état normal qu'un rôle de second plan. Mais à côté des résistances au flux aérien il en existe d'autres apparaissant dans le parenchyme pulmonaire lui-même à la suite des déformations tissulaires.

L'ensemble de ces résistances liées à l'intensité du flux aérien ont été réunies sous le nom de « viscance » par Bayliss et Robertson, terme que l'on peut traduire par « résistances visqueuses ».

Ainsi qu'on le voit, l'« élastance » est une fonction de la distension pulmonaire, c'est en quelque sorte une valeur statique alors que la viscosité dépend de phénomènes essentiellement dynamiques : l'intensité du flux aérien dans les canaux bronchiques et les déformations tissulaires jouant les rôles principaux.

Si nous enregistrons simultanément la pression œsophagienne ou pleurale et une courbe spirométrique ou pneumo-tachographique on peut établir un diagramme représentant les modifications de volume en fonction des variations de pression. Un tel diagramme nous permet de définir la valeur de l'« élastance » et de la « viscance » à chaque instant du cycle respiratoire. Mais chose beaucoup plus importante encore, un tel diagramme nous permet de mesurer graphiquement le travail nécessaire pour l'inspiration. Cette représentation graphique est à la base de la plupart des études sur la mécanique respiratoire et de la mesure du travail inspiratoire.

Si l'on réunit par une droite les deux points extrêmes de la courbe représentant le cycle respiratoire on aura un moyen de connaître à chaque instant la valeur de l'« élastance ». En effet ces deux points correspondent au passage de l'inspiration à l'expiration et inversement, le flux aérien étant nul à ces deux moments, cette droite permet de définir les variations de pression correspondant à une modification donnée du volume pulmonaire. Par contre l'aire de la courbe définissant le cycle respiratoire située au-dessus de cette droite caractérise les variations de la « viscance » au

cours de l inspiration grandeur qui comme je l ai dit depend uniquement de l intensite du flux aerien a l etat normal

A l etat physiologique le travail depense lors de la respiration est faible Il se calcule facilement a partir du diagramme volume/pression par determination graphique de l aire representant la somme de la « viscance » et de l « élastance » D apres Christie l organisme dépense environ 0 03 a 0 05 kg m par litre d air inspiré Environ 70 p 100 de ce travail est depensé pour vaincre les résistances elastiques alors que la « viscance » absorbe environ 30 p 100 dudit travail

Au moment de la crise d asthme le travail respiratoire augmente d une manière considérable il peut atteindre une valeur 12 fois supérieure a ce que l on observe à l état physiologique Cela n a rien d étonnant a premiere vue puisque des phénomenes de turbulen e ainsi que le montre l existence de sibilances tendent a jouer un role de premier plan au moment de l apparition de stenoses bronchiques Et nous savons que les resistances secondaires aux phénomènes de turbulence correspondent au carre du flux aérien et non pas a une simple proportionnalité comme cela est le cas lors des courants laminaires Mais ce qui est étonnant c est de voir que l elasticité du parenchyme pulmonaire s accroit aussi d une maniere souvent considérable au cours de la crise d asthme et c est la un phénomene qui n a pas eté étudié suffisamment On a voulu voir dans l elasticité pulmonaire une caractéristique en quelque sorte anatomique du tissu pulmonaire Cela est vrai lorsque le poumon forme un ensemble homogene et l elasticite a alors une signification essentiellement statique puisqu elle correspond aux forces de rétraction à deux états de distension bien definis quantitativement

Par contre au moment ou les canaux bronchiques ont des calibres tres variables d un territoire a l autre du poumon au moment ou les resistances au flux aérien varient d une maniere considérable selon les lobules pulmonaires consideres l *expansion se fera d une maniere non plus homogene* mais essentiellement inégale les territoires possedant des bronches bien [illegible]

Or cette inegalité dans l expansion inspiratoire sera d autant plus marquee que le flux aerien est plus intense On voit a cet instant que l elasticite pulmonaire tend a acquerir une signification dynamique puisqu elle depend de plus en plus de la vitesse du courant aérien dans les bronches C est pour cela qu a la notion d elasticité statique de la mécanique pulmonaire classique il faut opposer une élasticité dynamique ou effective qui est essentiellement sous la dependance du flux aérien intra bronchique Cette elasticite n a plus que des rapports lointains avec l élasticite en quelque sorte anatomique du poumon fonctionnant d une maniere homogène de l homme normal

La notion d « élastance » doit donc etre l objet d une revision sitot que l on considere la mecanique du poumon devenu heterogene a la suite de stenoses bronchiques Mais si l on regarde de pres les phénomenes qui apparaissent au cours de la crise d asthme on constate que la notion de viscosité devient aussi de plus en plus complexe En effet a l etat normal la viscosité n est que sous la dépendance de l intensite du flux aérien alors que lors de la crise d asthme le degre de distension pulmonaire prend une

importance de plus en plus considérable pour les valeurs des résistances visqueuses En effet alors que la viscosité ne varie que peu à l'état normal selon les degrés de distension pulmonaire on observe en cas d'asthme une augmentation brusque de la viscosité au moment de l'expiration les valeurs positives de pression qui apparaissent dans le thorax à ce moment ayant tendance à sténoser davantage les canaux aériens

En résumé l'asthme transforme entièrement la mécanique respiratoire puisque l'élasticité devient en partie une fonction du flux aérien et la viscosité tend à passer sous l'influence du degré de distension pulmonaire Les calculs indiquent que l'augmentation de la viscosité est responsable de 55 p 100 de l'accroissement du travail respiratoire lors de la crise d'asthme 45 p 100 dépendant d'une élévation de l'élasticité ce qui montre entre autres que l'élasticité en devenant dynamique est un facteur fort important de l'augmentation du travail lors de la crise asthmatique

Ce n'est que si l'on définit avec précision les termes que l'on utilise pour caractériser les diverses fonctions mécaniques du poumon que l'on peut comprendre les altérations de la dynamique pulmonaire au cours de l'asthme

On a beaucoup discuté de l'origine de la dyspnée de l'asthmatique On l'a attribuée à l'hyperventilation aux modifications des gaz du sang à la surcharge du cœur droit à l'angoisse etc Or si l'on regarde de près les choses on constate que la dyspnée de l'asthmatique est la traduction subjective de l'augmentation du travail respiratoire Elle est donc liée étroitement à l'apparition d'une hétérogénéité fonctionnelle du poumon puisque c'est à ce facteur que l'on doit attribuer essentiellement les excès de dépenses énergétiques de l'asthmatique Comme on le voit l'étude de la mécanique respiratoire conduit à la solution d'un problème essentiellement clinique le problème de la dyspnée

RÉSUMÉ

Les troubles de la ventilation pulmonaire sont bien connus actuellement lors de la crise d'asthme et de l'emphysème On peut observer au cours de l'asthme par exemple une hyperventilation alvéolaire une insuffisance partielle liée à un trouble de distribution ou une hypoventilation alvéolaire L'hypertension dans la petite circulation n'apparaît en thèse générale que si une hypoventilation alvéolaire se développe

La nature des troubles de la mécanique respiratoire lors de l'asthme et de l'emphysème n'a été élucidée qu'au cours de ces dernières années Les muscles respiratoires doivent surmonter deux sortes de résistance les résistances élastiques et celles dites visqueuses Les résistances élastiques sont liées à l'état normal aux variations de volume pulmonaire alors que les résistances visqueuses sont essentiellement des fonctions de l'intensité du flux aérien Lors de la crise d'asthme la « viscance » augmente considérablement à la suite des sténoses bronchiques Mais il en est de même de l' « élastance » En effet les sténoses bronchiques entraînent une hétérogénéité fonctionnelle pulmonaire les territoires à bronches plus ou moins libres se distendant lors de l'inspiration d'une manière beaucoup plus marquée que les territoires où les bronches sont le siège de sténoses serrées

Cette hétérogénéité pulmonaire entraine une augmentation de l'index d'élasticité et cet accroissement sera d'autant plus marqué que le flux aérien sera plus intense. Lors de l'asthme et de l'emphysème obstructif l'élasticité pulmonaire acquière donc un aspect dynamique que l'on n'observe pas lorsque l'on étudie le poumon sain. La dyspnée de l'asthmatique et de l'emphysémateux est étroitement liée à l'augmentation du travail respiratoire, c'est à dire aux variations de l'élastance et de la viscance.

SUMMARY

Ventilation disturbances occurring during asthmatic and emphysematous crises are well known to-day.

In asthma, for example, an alveolar hyperventilation and also a partial inadequacy linked to a distribution disturbance or alveolar hypoventilation are observed. High blood pressure in the small circulation system generally only appears in the case of developing alveolar hypoventilation.

The nature of the disturbances of the breathing process has only been ascertained during the last passed years.

Respiratory muscles have to overcome two sorts of resistances: the elastic and the so called « viscous one ».

In normal conditions, elastic resistances are linked to the changes of the pulmonary volume, whereas viscous resistances essentially depend on the intensity of the aerial flow.

During the asthmatic crises the « viscance » greatly increases on account of bronchial stenosis which is also true for the « elastance ».

In fact, bronchial stenosis brings about a functional pulmonary heterogeneity: during the in breathing territories where the bronchi are more or less free, expand in much broader way as territories where close stenosis are located.

This pulmonary heterogeneity entails an increase of the elasticity index and its increase follows the chanes of intensity of the aerial flow.

During asthma and obstructive emphysema, pulmonary elasticity gains a dynamic aspect not observable in a normal lung.

The dyspnea of asthmatic and emphysematous subjects is closely linked to the increase of the respiratory functional work, this means to the changes of the « elastance » and the « viscance ».

ZUSAMMENFASSUNG

Während der Asthma- und Emphysemkrisis auftretende Ventilationsstörungen sind heute gut bekannt.

Bei Asthma zum Beispiel kann man eine alveolare Hyperventilation und auch teilweises Versagen, verbunden mit einer Verteilungsstörung oder alveolaren Hypoventilation beobachten. Bluthochdruck im kleinen Kreislauf tritt im allgemeinen nur bei einer sich entwickelnden alveolaren Hypoventilation auf.

Die Natur der Störungen des Atemmechanismus wurde erst in den letzten Jahren ermittelt.

Die Atemmuskeln mussen zwei Arten von Widerstanden uberwinden einen elastischen und einen sogenannten viskosen

Normalerweise ist der elastische Widerstand gekoppelt mit den Veranderungen des Lungenvolumens wahrend der viskose Widerstand im wesentlichen von der Intensität des Luftzustromes abhangt

Wahrend der Asthmakrisis nimmt die Viscance wegen der Bronchial stenose sehr stark zu dasselbe gilt fur die Elastance'

In der Tat bringt die Bronchialstenose eine pulmonare Funktionshete rogenitat mit sich wahrend des Einatmens dehnen sich diejenigen Lungen partien viel starker aus in denen die Bronchien mehr oder weniger frei sind als die Partien mit starken Stenosen

Diese Lungenheterogenitat bewirkt eine Zunahme des Elastizitats Index und diese Zunahme folgt den Veranderungen der Intensitat des Luftzus tromes

Wahrend des Asthma und des obstruktiven Emphysems bekommt die Lungenelastizitat einen dynamischen bei normalen Lungen nicht zu beobachtenden Aspekt

Die Dyspnoe von Asthmatikern und Emphysemkranken ist eng mit der Zunahme der Atemfunktion verbundern das heisst mit den Anderungen der ' Elastance und Viscance

RESUMEN

Los trastornos de la ventilación pulmonar durante las crisis de asma y de enfisema son actualmente bien conocidos Durante la crisis asmática, por ejemplo pueden observarse, ya sea una hipertensión alveolar una insuficiencia parcial unida a un trastorno de la distribución o una hipoventilación alveolar La hipertensión en la pequeña circulación en general no aparece mas que cuando se produce una hipoventilación alveolar

La naturaleza de las alteraciones de la mecánica respiratoria durante el asma y el enfisema ha sido aclarada recién en los ultimos años Los musculos respiratorios deben vencer dos tipos de resistencia las resistencias elásticas y las llamadas viscosas Las resistencias elásticas están vinculadas en el estado normal a las variaciones de volumen pulmonar en tanto que las resistencias viscosas son esencialmente función de la intensidad del flujo gaseoso Durante la crisis de asma la «viscancia» aumenta considerablemente como consecuencia de las estenosis bronquiales Pero lo mismo sucede con la «elastancia» En efecto las estenosis bronquiales conducen a una hetero geneidad funcional pulmonar pues durante la inspiración las zonas donde los bronquios están mas o menos libres se distienden de manera mucho más marcada que las zonas donde hay una estenosis importante Esta hetero geneidad provoca un aumento del índice de elasticidad aumento que es mas pronunciado cuanto más intenso es el flujo gaseoso Por lo tanto durante el asma y el enfisema obstructivo la elasticidad pulmonar adquiere un carác ter dinámico que no existe en el pulmón sano La disnea del enfermo asmá tico o enfisematoso está estrechamente vinculada al aumento del trabajo respiratorio es decir a las variaciones de la elastancia» y la «viscancia»

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ANALYSE, MESURE ET RÔLE DES FACTEURS RÉGISSANT LES PERTURBATIONS FONCTIONNELLES PULMONAIRES DE L'ASTHMATIQUE

par

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A l'origine des perturbations fonctionnelles pulmonaires de l'asthmatique deux processus jouent un rôle prépondérant.

1° *L'allergie pulmonaire*. Elle a pour effet, au terme des réactions antigènes-anticorps, de produire des médiateurs à activité bronchoconstrictive (histamine).

2° *L'excitabilité accrue des effecteurs moteurs pulmonaires* (muscles lisses des bronches et des vaisseaux, glandes) vis-à-vis de leurs médiateurs physiologiques (acétylcholine) et pathologiques (histamine) : *hypersensibilité pulmonaire cholinergo-histaminique*. Il s'y ajoute souvent une *hyperexcitabilité des terminaisons sensitives pulmonaires* (récepteurs sensitifs) génératrice de *réflexes bronchoconstrictifs*.

Ces deux processus qui conjuguent leurs effets pour produire des actions bronchoconstrictives asthmogènes n'ont pas une évolution parallèle, mais au contraire inverse : l'allergie pulmonaire tend à s'atténuer, l'hypersensibilité cholinergo-histaminique à s'accroître avec l'âge du sujet et l'ancienneté de la maladie.

Aussi les degrés de ces deux processus sont-ils très différents d'un asthmatique à un autre et fournissent-ils une grande variété de combinaisons ; celles-ci cadrent bien avec les divers aspects cliniques de la maladie.

La sensibilité cholinergo-histaminique, l'excitabilité des récepteurs sensitifs et l'allergie pulmonaire peuvent se mesurer. Les résultats de ces mesures, les déductions qui en ont été tirées font l'objet de cet exposé.

HYPEREXCITABILITÉ DES EFFECTEURS MOTEURS PULMONAIRES (HYPERSENSIBILITÉ PULMONAIRE CHOLINERGO HISTAMINIQUE)

Elle se mesure et s exprime par la plus petite dose (dose liminaire) d un agent bronchoconstrictif (acétylcholine histamine) nécessaire pour produire une perturbation ventilatoire tangible (effet seuil) (1 2)

La *dose liminaire* est détectée par des essais successifs au cours desquels sont administrés sous forme d aerosols des doses croissantes d acétyl choline ou d histamine L *effet seuil* consiste en une diminution d amplitude du tracé spirographique du cycle ventilatoire maximum

La sensibilité pulmonaire cholinergo histaminique est accrue chez tous les asthmatiques (3) des mesures ont eté effectuees chez pres de 1 000 asth matiques

Son degré differe d un asthmatique a un autre dans des proportions consi dérables (4) Chez les asthmatiques les plus sensibles la D L (*) d acétyl choline (**) n excede pas quelques μg chez les moins sensibles qui confinent aux sujets normaux la D L Ac atteint plusieurs milliers de μg

[illegible]

a des agressions bronchoconstrictives de plus en plus minimes d assurer une action asthmogene (6)

Sa mesure présente un intéret pratique (diagnostique et thérapeutique) certain (7)

L hypersensibilité pulmonaire cholinergo histaminique est de toute évidence l expression d un substratum pathologique fondamental de la maladie asthma tique

HYPEREXCITABILITÉ DES RÉCEPTEURS SENSITIFS PULMONAIRES

L excitabilite des terminaisons sensitives pulmonaires s etudie en mettant a profit la propriété que possede l acétylcholine d exciter les récepteurs sensitifs (8) d ou une réaction tussigene Les deux actions excito sensitive et bronchomotrice de l acétylcholine sont distinctes et differenciables les V et VI méthoniums empechent la premiere non la seconde (9)

L excitabilite des terminaisons sensitives pulmonaires peut etre mesuree (10) elle s exprime par la plus faible concentration d un aérosol d acé tylcholine dont l inhalation déclenche une reaction de toux

Il resulte d une etude portant sur 105 asthmatiques que 60 9 p 100 d entre eux ont une hyperexcitabilite des terminaisons sensitives pulmonaires (10) Celle ci tend a s accentuer au fur et a mesure que l asthme devient plus ancien et s aggrave

* D L dose liminaire Ac acétylcholine

** La D L d histamine est un peu plus basse que la D L Ac (5)

Les dispositifs sensitifs pulmonaires sont excités par des agents véhiculés par l'atmosphère ambiante (air froid, particules irritantes dispersées dans l'air). L'excitation produite peut déclencher un réflexe bronchoconstrictif (10).

Ainsi chez nombre d'asthmatiques les agressions irritantes constituent un facteur asthmogène. Il peut être rapproché de celui que constituent les agressions allergéniques. Les deux ordres d'agents agressifs sont véhiculés par l'air; tous deux induisent une perturbation ventilatoire: les premiers (agents irritants) par le jeu d'un réflexe bronchoconstrictif, les seconds (agents allergiques) par l'intervention de médiateurs bronchoconstrictifs. Les agressions allergéniques interviennent davantage dans les formes récentes de la maladie, les agressions irritantes dans les formes anciennes. Ces deux ordres d'agression peuvent cependant s'associer ou se relayer.

SENSIBILITÉ PULMONAIRE ALLERGÉNIQUE ET ALLERGIE PULMONAIRE

Chez l'asthmatique sensibilisé à un pneumallergène, l'inhalation d'un dispersat de cet allergène produit un effet ventilatoire analogue à celui qu'exerce l'acétylcholine ou l'histamine (11).

[illegible]

seuil) (7).

On entend par *allergie pulmonaire* (12) l'ensemble des processus qui, déclenchés par un apport d'allergènes (inhalation d'une préparation d'allergènes), aboutissent à l'excitation des effecteurs moteurs pulmonaires (bronchoconstriction). Il est admis que cette excitation s'effectue par l'intermédiaire de médiateurs (histamine). Le degré de l'allergie pulmonaire peut donc être exprimé par la *quantité de médiateurs bronchoconstrictifs engendrés par une quantité déterminée d'allergènes*.

Le degré de l'allergie pulmonaire peut être mesuré à partir de la D.L. (*) d'une préparation d'allergènes et de la D.L. d'un agent bronchoconstrictif (acétylcholine ou histamine). Ces deux doses produisent, par définition, le même effet ventilatoire: effet seuil. On peut en déduire que la D.L. d'allergènes A engendre une quantité de médiateurs dont l'activité bronchoconstrictive est identique à celle qu'exerce la D.L. d'acétylcholine B ou la D.L. d'histamine B1. Il en résulte qu'une unité pondérale (1 µg) de la préparation d'allergènes administrée engendre une quantité de médiateurs dont l'activité bronchoconstrictive équivaut à celle qu'exerce B/A µg d'acétylcholine ou B1/A µg d'histamine.

Ainsi les quotients B/A, B1/A qui expriment, le premier en µg d'acétylcholine, le second en µg d'histamine, l'activité pharmacodynamique bronchoconstrictive de la quantité de médiateurs libérés par un µg de la préparation d'allergènes, sont bien représentatifs du degré de l'allergie pulmonaire pour l'allergène considéré.

La *spécificité antigénique de l'effet ventilatoire* produit par l'inhalation d'allergènes a été vérifiée par des contrôles de divers ordres (12). D'autres

* Dose liminaire.

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Elle se mesure et s'exprime par la plus petite dose (dose liminaire) d'un agent bronchoconstrictif (acétylcholine, histamine) nécessaire pour produire une perturbation ventilatoire tangible (effet seuil) (1, 2).

La *dose liminaire* est détectée par des essais successifs au cours desquels sont administrés, sous forme d'aérosols, des doses croissantes d'acétylcholine ou d'histamine. L'*effet seuil* consiste en une diminution d'amplitude du tracé spirographique du cycle ventilatoire maximum.

La sensibilité pulmonaire cholinergo-histaminique est accrue chez tous les asthmatiques (3) : des mesures ont été effectuées chez près de 1 000 asthmatiques.

Son degré diffère d'un asthmatique à un autre dans des proportions considérables (4). Chez les asthmatiques les plus sensibles, la D.L. (*) d'acétylcholine (**) n'excède pas quelques μg ; chez les moins sensibles, qui confinent aux sujets normaux, la D.L.Ac. atteint plusieurs milliers de μg.

Elle précède l'apparition des premiers symptômes de la maladie (détection d'un asthme latent) (3). Elle persiste dans l'intervalle des poussées (3). Elle s'accentue au fur et à mesure que l'asthme s'aggrave, fait essentiel qui permet à des agressions bronchoconstrictives de plus en plus minimes d'assurer une action asthmogène (6).

Sa mesure présente un intérêt pratique (diagnostique et thérapeutique) certain (7).

L'hypersensibilité pulmonaire cholinergo-histaminique est de toute évidence l'expression d'un substratum pathologique fondamental de la maladie asthmatique.

HYPEREXCITABILITÉ DES RÉCEPTEURS SENSITIFS PULMONAIRES

L'excitabilité des terminaisons sensitives pulmonaires s'étudie en mettant à profit la propriété que possède l'acétylcholine d'exciter les récepteurs sensitifs (8), d'où une réaction tussigène. Les deux actions excito-sensitive et bronchomotrice de l'acétylcholine sont distinctes et différenciables : les V et VI méthoniums empêchent la première, non la seconde (9).

L'excitabilité des terminaisons sensitives pulmonaires peut être mesurée (10) : elle s'exprime par la plus faible concentration d'un aérosol d'acétylcholine dont l'inhalation déclenche une réaction de toux.

Il résulte d'une étude portant sur 105 asthmatiques que 60,9 p. 100 d'entre eux ont une hyperexcitabilité des terminaisons sensitives pulmonaires (10). Celle-ci tend à s'accentuer au fur et à mesure que l'asthme devient plus ancien et s'aggrave.

* D.L. : dose liminaire ; Ac. : acétylcholine.

** La D.L. d'histamine est un peu plus basse que la D.L.Ac. (5).

seconde éventualité il ne se produit qu'une *atténuation* plus ou moins sensible de l'état asthmatique l'allergie n'étant plus qu'un *facteur asthmogène accessoire* (12)

Il est possible que des relations de causalité unissent les deux processus fondamentaux qui font l'objet de cette étude l'allergie pulmonaire et l'hypersensibilité cholinergo histaminique du poumon asthmatique

On peut en effet se demander si les médiateurs engendrés par les réactions allergiques ne peuvent du fait des excitations réitérées et excessives auxquelles ils soumettent les effecteurs moteurs pulmonaires (muscles lisses bronchiques et vasculaires) accroître l'excitabilité de ces derniers et ainsi être à l'origine de l'hypersensibilité cholinergo histaminique ou la favoriser

RÉSUMÉ

Deux processus régissent les perturbations fonctionnelles pulmonaires de l'asthme

1° *L'allergie pulmonaire* qui engendre des médiateurs bronchoconstrictifs (histamine)

2° *La sensibilité pulmonaire accrue aux actions bronchoconstrictives* exercées en particulier par les médiateurs physiologiques (acétylcholine) et pathologiques (histamine) des effecteurs moteurs qui régissent le mécanisme ventilatoire interne (jeu broncho alvéolaire) A cette *hypersensibilité cholinergo-histaminique* s'ajoute souvent une *hyperexcitabilité des terminaisons sensitives pulmonaires* (récepteurs sensitifs) génératrices de *réflexes bronchoconstrictifs*

L'hypersensibilité cholinergo histaminique est l'expression d'un *substratum pathologique fondamental de l'asthme* On l'observe chez tous les asthmatiques Elle s'*accentue* au fur et à mesure que l'asthme *s'accroît* et peut devenir considérable

Chez la quasi totalité des asthmatiques une *sensibilisation allergique*

n'est forte que dans 1/3 des cas En outre elle tend à régresser avec l'âge et l'ancienneté de l'asthme

Les actions asthmogènes qu'exerce l'allergie pulmonaire par l'intermédiaire des médiateurs bronchoconstrictifs sont subordonnées au degré de la sensibilité cholinergo histaminique pulmonaire Ainsi une forte allergie pulmonaire n'est pas asthmogène si l'hypersensibilité cholinergo histaminique est faible (asthme latent asthme récent)

Lorsque cette hypersensibilité s'accroît des agressions allergéniques minimes (donc nombreuses) deviennent asthmogènes Mais le deviennent aussi divers facteurs bronchoconstrictifs non allergéniques qui assurent désormais l'entretien de l'asthme tandis que l'asthme pulmonaire peut s'atténuer ou s'éteindre

La régression (désensibilisation) de l'allergie pulmonaire a des consé

quences très différentes selon qu'elle se produit avant ou après que se soit constituée une forte hypersensibilité cholinergo histaminique.

Les manifestations asthmatiques peuvent disparaître dans le premier cas (l'allergie était prépondérante); elles s'atténuent seulement dans le second cas (l'allergie n'est plus qu'un facteur asthmogène accessoire).

SUMMARY

Functional disturbances of the lung in asthma are conditioned by two processes:

1° pulmonary allergy responsible for the production of broncho-constrictor mediators (Histamine).

2° increased pulmonary sensitivity of the effectors either to the physiological mediator (acetyl choline) or the pathological one (Histamine) which control the mechanism of the pulmonary ventilation (alveolo bronchial action). To this hypersensitivity to cholinergic and histaminic mediators one should add the hyper excitability of pulmonary sensory nerve endings (sensitive receptors) responsible for certain broncho constrictor reflexes. The cholinergic and histaminic hypersensitivity determine a fundamental pathological asthmatic substratum. This occurs in all cases of asthma. It develops with the asthma and may become prevalent.

In almost all asthmatic patients allergic pulmonary sensitivity has been found. But the degree of pulmonary allergy (amount of broncho constrictor mediators produced for a given quantity of allergens) is very different from one individual to another. Strong pulmonary allergy only occurs in one third of the cases. Besides it tends to decrease with age and the longer duration of the disease.

Asthmogenic actions exerted by pulmonary allergy by means of it's broncho constrictor mediators depends on the degree of pulmonary cholinergo histaminic sensitivity. Therefore a strong pulmonary allergy is not asthmogenic if the cholinergo histaminic hypersensitivity is slight (Latent asthma, recent asthma).

As this hypersensitivity increases minor allergy aggressors become asthmogenic. But other various and non allergic broncho constrictor factors become asthomogenic too and from now on keep asthma up whereas pulmonary allergy may diminish or disappear.

The regression (desensitization) of pulmonary allergy may have very different consequences whether it occurs before or after the setting in of a strong cholinergo histaminic hypersensitivity.

Asthmatic symptoms may disappear in the first case (when allergy is prevalent) and only diminish in the second case (when allergy is only an accessory asthmogenic factor).

ZUSAMMENFASSUNG

Zwei Prozesse lenken die funktionellen Störungen der Lunge beim Asthma.

1° *Die Lungenallergie* welche die bronchoconstructiven Vermittler hervorbringt (Histamin).

2° *Die Sensibilität der Lunge zusätzlich zu den broncho konstrictiven Aktionen* welche besonders durch die physiologischen (Acetylcholin) und pathologischen (Histamin) Vermittler bewirkt wird die den internen Ventilationsmechanismus lenken (broncho alveolares Spiel) Zu dieser *cholinergo-histaminen Hypersensibilität* tritt häufig noch eine *Hyperexcitabilität der* [illegible]) welche die *broncho co*[illegible]

[illegible] Ausdruck eines *funda me*[illegible] Man kann sie bei allen Asthmatikern beobachten Sie *verstärkt* sich in dem Masse in dem das Asthma *anwächst* und kann beachtliche Ausmasse annehmen

Bei fast allen Asthmatikern wurde eine *allergische Sensibilität der Lunge* festgestellt Aber der Grad der Lungenallergie (Quantität der bronchoconstrictiven Vermittler die von einer bestimmten Menge von Allergenen erzeugt wird) ist *sehr unterschiedlich bei den einzelnen Patienten* Die Lungenallergie kommt nur in einem Drittel der Fälle verstärkt zur Auswirkung Sie tendiert dazu mit dem Alter des Patienten und der Dauer des Asthmas zurückzugehen

Die asthmogenen Aktionen welche die Lungenallergie mittels der bronchokonstrictiven Vermittler ausübt sind von dem Grad der cholinergo histaminen Sensibiltät der Lunge abhängig Daher wirkt eine starke Lungenallergie nicht asthmogen wenn die cholinergo-histamine Hypersensibi[illegible]

[illegible] werden die geringsten allergenen [illegible] aber auch gewisse nicht allergene bronchoconstrictive Faktoren werden es und sorgen weiterhin dafür dass das Asthma andauert während das Lungenasthma zurückgehen oder ganz verschwinden kann

Die Regression (Desensibilisierung) der Lungenallergie hat sehr verschiedene Folgen je nachdem ob sie vor oder nach dem Zeitpunkt erfolgt zu dem sich eine cholinergo histamine Hypersensibilität eingestellt hat

Im ersten Fall können die Anzeichen des Asthmas verschwinden wenn die Allergie vorherrscht Im zweiten Fall können sie sich nur verringern die Allergie ist hier nur ein nebensächlicher Faktor

RESUMEN

Las perturbaciones funcionales pulmonares del asma están determinadas por dos factores

1° *La alergia pulmonar* que produce mediadores broncoconstrictores (histamina)

2° *El aumento de la sensibilidad pulmonar a las acciones broncoconstrictoras* ejercidas en particular por los mediadores fisiológicos (acetilcolina) y patológicos (histamina) de los efectores motores que regulan el mecanismo de de ventilación interna (juego bronco alveolar A esta *hipersensibilidad colinergo histamínica* se agrega a menudo una *hiperexcitabilidad de las terminaciones sensitivas pulmonares* (receptores sensitivos) generadora de *reflejos broncoconstrictores*

La hipersensibilidad colinergo histamínica es la expresión de un *sustrato*

patológico pulmonar fundamental del asma Se la observa en todos los asmáticos y se acentua a medida que el asma *aumenta* pudiendo llegar a ser considerable

En la casi totalidad de los asmáticos ha podido detectarse una *sensibilización alérgica pulmonar* Pero el *grado de alergia pulmonar* (cantidad de mediadores broncoconstrictores producidos por una cantidad determinada de alergenos) es *muy diferente de un individuo a otro* La alergia pulmonar es intensa solamente en un tercio de los casos Además tiende a disminuir con la edad y la antiguedad del asma

Las acciones asmógenas que ejerce la alergia pulmonar por intermedio de los mediadores broncoconstrictores están subordinadas al grado de sensibilidad colinergo histamínica pulmonar De esta manera una fuerte alergia pulmonar puede no ser asmógena si la hipersensibilidad colinergo-histamínica es leve (asmas latentes asmas recientes)

Cuando esta hiper sensibilidad aumenta las agresiones alergenicas mínimas (y por lo tanto numerosas) se transforman en asmógenas y lo mismo ocurre con diversos factores broncoconstrictores no alergénicos que aseguran en lo sucesivo el mantenimiento del asma mientras que la alergia pulmonar puede atenuarse o desaparecer

La regresión (desensibilizac on) de la alergia pulmonar tiene consecuencias muy diferentes segun que ella se produzca antes o después del establecimiento de una fuerte hipersensibilidad colinergo histamínica

Las manifestaciones asmáticas pueden desaparecer en el primer caso (cuando la alergia es preponderante) en el segundo caso (cuando la alergia no es mas que un factor asmógeno accesorio) solamente llegan a atenuarse

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MODIFICATIONS DE LA CIRCULATION PULMONAIRE DANS L ASTHME ET L EMPHYSÈME L HYPERTENSION ARTÉRIELLE PULMONAIRE

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Les troubles de la circulation pulmonaire dans l asthme ont été l objet de divers travaux concernant quelques uns l asthme lui meme la plupart les conditions broncho-pulmonaires auxquelles l asthme se trouve souvent mele notamment l emphyseme pulmonaire

Ces troubles sont actuellement connus Le plus important d entre eux parait etre l hypertension artérielle pulmonaire dont le mecanisme en dépit de nombreuses études reste controversé le role respectif des lésions anatomiques et des troubles fonctionnels des arteres et artérioles pulmonaires a été diversement apprécié par les differents auteurs qui se sont préoccupés de la question

Le but de ce travail est de préciser la part de chacun de ces deux processus à l aide de corrélations entre les données cliniques physiologiques et anatomiques

MATÉRIEL

102 malades atteints d emphyseme avec ou sans asthme constituent le matériel de cette étude 88 sont des hommes 14 des femmes et leur âge moyen est de 48 ans 4 mois (ages extremes 15 ans et 72 ans) Suivant l étiologie ces malades se repartissent de la façon suivante

17 ont des asthmes primitifs datant de l enfance compliqués plus ou moins tardivement de catarrhe bronchique avec emphyseme

85 ont une maladie broncho pulmonaire primitive dont 40 se sont compliquées d asthme plus ou moins précocement

Ces 102 malades ont subi 116 explorations fonctionnelles circulatoires Suivant l état clinique dans lequel se trouvaient ces patients au moment du cathéterisme quatre groupes peuvent etre distingués

Groupe I malades sans hypertension artérielle pulmonaire et n ayant aucun signe passé ou présent d insuffisance cardiaque 12 explorations
Gr[illegible]
sance cardiaque 35 explorations
Groupe III malades dont les signes cliniques d insuffisance cardiaque ont disparu au moment du cathétérisme 39 explorations
Groupe IV malades ayant au moment de l exploration des signes cliniques d insuffisance cardiaque en évolution 30 explorations

La discrimination est aisée entre les groupes I II et l ensemble des groupes III et IV Elle peut etre difficile entre les groupes III et IV En effet lors du traitement d une insuffisance cardiaque la régression des altérations hemodynamiques précède de plusieurs jours la régression des signes cliniques De sorte qu un patient dont les signes cliniques d insuffisance cardiaque sont encore tres nets peut avoir s il a déja subi un début de traitement une amélioration considerable des constantes hémodynamiques Aussi est il probable que nombre de cas classés ici dans le groupe IV du fait de leurs signes cliniques appartiennent dejà au groupe III par leurs signes hémodynamiques

MÉTHODE D ÉTUDE

Ces explorations circulatoires ont été effectuées selon la technique habituelle (Scebat et collaborateurs) Dans 25 cas une epreuve d effort a ete pratiquee selon une méthode décrite ailleurs (Bourgain et collaborateurs) Chez 20 malades le volume sanguin a éte mesuré par la méthode de dilution du bleu (technique de Cachera et Barbier) L action de l inhalation d oxygene pur a eté étudiée chez 23 malades l action d un vasodépresseur chez 8 patients Enfin des observations ont été faites au cours de crises d asthme spontanées (3 malades) ou provoquées par aérosols d acetyl choline (3 malades)

Ces études hémodynamiques ont été complétees dans 11 cas par une angiocardiographie visant à préciser l état de l arbre arteriel pulmonaire

Une etude anatomique a pu etre faite chez 12 des 102 patients explores Cette étude limitée a l examen des artères pulmonaires a été conduite systématiquement de la façon suivante chaque fragment de lobe prélevé est examine en notant separément l état des artérioles (d un diametre inferieur a 100 μ) des petites arteres (d un diametre compris entre 100 μ et 2 mm) des arteres (d un diamètre superieur a 2 mm) Sur chaque coupe correspondant a un lobe vingt vaisseaux de chaque catégorie sont examines quant aux altérations intimales médiales ou adventitielles Ainsi est etabli pour cent vaisseaux de chaque categorie le pourcentage d artères de petites arteres ou d artérioles lésées De plus le degre de stenose est apprecie par le calcul du rapport $\frac{\text{epaisseur de la paroi}}{\text{diamètre du vaisseau}}$ Un rapport superieur a 1/5 est considére anormal

49905

RÉSULTATS

1° *Les résultats hémodynamiques* sont résumés dans le tableau I Ils mon trent lorsqu on passe ... une

une

une

ation

progressive de la pression et de la résistance artérielles pulmonaires

2° *Les résultats de l épreuve d effort* sont résumés dans le tableau II L index cardiaque augmente de façon normale sauf au stade IV La pression artérielle pulmonaire s élève nettement aux stades II III et IV La résistance pulmonaire ne subit d accroissement important qu au stade IV

3° ... tableau III

e

de la résistance artérielle pulmonaire pour les malades du stade II Aux stades III et IV la chute de pression accompagne une diminution de l index cardiaque

4° *Des angiocardiographies* ont été prises chez 11 malades Trois de ces malades appartiennent au groupe I 3 au groupe II 2 au groupe III et 3 au



Fig 1 — Angiocardiographie chez un sujet normal montrant la circulation artérielle pulmonaire P A P M = 12 mm Hg

groupe IV Sept clichés (fig 2 3 4 5 6 7 et 8) sont reproduits en regard d un huitième cliché pris chez un sujet normal (fig 1) Ces clichés montrent

Tableau I

Valeurs de diverses constantes hémodynamiques à l'état basal aux divers stades de l'évolution de la maladie broncho pulmonaire et du cœur pulmonaire chronique

	Capacité en cm			Hématocrite			Volume plasma en cm			Saturation artérielle périphérique			Index card l mn m²			PCPM mm/Hg	PAP mm Hg			PADM mm/Hg	RAP dynes/cm⁵ sec		
	moy	min	max	moy	min	max	moy	min	max	moy	min	max	moy	min	max		moy	min	max		moy	min	max
Normaux	19 5	15 3	24	42 5	37 5	46 5	2 600	1 690	3 210	95 6	91 1	99	3 59	2 20	4 83	6	11 5	8 5	14 5	1	146	106	205
Groupe I	19 5	17 2	25 4							91 7	85 5	98	3 82	2 50	7 95	4	11 2	6	14 7	1 5	127	79	216
Groupe II	21 2	14 7	27	48 4	46 8	50	2 050	2 040	2 060	87 6	70	98 5	3 10	1 85	5 52	4	19 6	11 8	36 1	0 8	342	130	725
Groupe III	21 7	14 6	26 6	54	50 8	59 1	2 436	1 970	2 770	83 7	60 1	99 3	3 42	1 86	6 5	3 5	27 7	11 5	50	0 8	436	124	850
Groupe IV	23	15 6	28 3	55 5	52 8	58 8	3 250	2 370	4 050	74 4	43 3	93 4	3 96	2 06	7 21	4	38	20 6	63	7 6	517	186	1 108

PAPM = Pression Artérielle Pulmonaire Moyenne
PCPM = Pression Capillaire Pulmonaire Moyenne
PADM = Pression Auriculaire Droite Moyenne
RAP = Résistance Artérielle Pulmonaire

Moy = moyenne
Min = minima
Max = maxima

TABLEAU II

Action de l'effort sur les diverses constantes hémodynamiques selon les divers stades évolutifs de la maladie broncho-pulmonaire et du cœur pulmonaire chronique

		NOMBRE DE CAS	P A P M mm de mercure	SAT ART PÉRIPH en	INDEX CARDIAQUE		R A P dynes cm⁻⁵ s c
					l mn m²	Augm p 100	
Normaux	C Eff Var	5	12 13 + 8 4	97 2 96 5 — 0 7	3 49 6 18 + 77	630	130 102 — 21 5
Groupe I	C Eff Var	2	10 10 0	98 98 8 + 0 8 %	3 4 8 + 60	605	182 89 — 51
Groupe II	C Eff Var	9	16 23 6 + 4 5	89 7 91 6 + 2 2	3 4 5 55 + 63	620	235 212 — 9 8
Groupe III	C Eff Var	13	26 6 42 8 + 61	86 9 84 6 — 2 7	3 3 4 9 + 48 5	500	413 482 + 16 7
Groupe IV	C Eff Var %	2	25 40 + 60	79 3 86 2 + 8 7	4 93 5 29 + 7 3	204	263 415 + 58

C = contrôle Eff = effort Var = variation Augm p 100 = augmentation de l'index cardiaque pour 100 cm d'accroissement du métabolisme basal



FIG 2 — Angiocardiographie chez une asthmatique de 20 ans Cœur normal P A P M = 12 mm Hg Aspect sensiblement normal de la circulation pulmonaire sauf dans le lobe supérieur gauche où les artères sont moins bien injectées

TABLEAU III

Action de l oxygène sur la circulation selon les différents stades du cœur pulmonaire chronique

		NOMBRE DE CAS	SATURATION ART PÉRIPH	P A P M mm Hg	INDEX CARDIAQUE l mn m	RÉSISTANCE ART PULM dynes/cm sec
Groupe II	Contrôle Oxygène Variation (p 100)	6	82 3 102 5 + 24 6	24 6 22 8 — 6 5	2 5 2 5 0	640 398 — 37 9
Groupe III	Contrôle Oxygène Variation (p 100)	10	80 101 9 + 27 4	31 1 27 1 — 12 9	3 48 3 — 13 8	474 443 — 6 6
Groupe IV	Contrôle Oxygène Variation (p 100)	7	76 7 103 + 34	36 1 31 1 — 13 9	4 18 2 87 — 31 4	535 549 + 2 6

pour les malades du stade I un aspect sensiblement normal des artères pulmonaires. Pour les malades des trois autres groupes l'aspect filiforme des artères pulmonaires périphériques s'oppose à la dilatation du tronc et des branches proximales de l'artère pulmonaire. Il n'y a pas de différences marquées entre les trois groupes. Chez 6 malades cet aspect filiforme des



FIG. 3. — Angiocardiographie chez une emphysémateuse de 50 ans. Stade initial du cœur pulmonaire chronique. P.A.P.M. = 30 mm Hg. Dilatation du tronc et des branches hilaires. Mauvaise injection des artères à la périphérie sauf dans les sommets des deux poumons.

artères pulmonaires périphériques est également réparti à l'ensemble des poumons; chez deux autres il existe des zones où l'aspect de constriction est plus marqué que pour l'ensemble des deux plages pulmonaires.

5° *Les résultats des examens anatomiques* sont résumés dans le tableau IV. Dans sept cas les altérations intéressent de 5 à 40 % des artères ou des artérioles; dans cinq cas 50 % ou plus des petites artères ou des artérioles sont lésées.

Dans onze cas sur douze la *lésion essentielle est musculaire*: il s'agit soit d'hypertrophie de la média des petites artères (fig. 9), soit d'infiltration de cellules musculaires dans l'intima de ces mêmes artères (fig. 10), soit

musculaires Dans un cas l adventice est la seule tunique lésée infiltrée de sclérose (fig 12)



FIG 4 — Angiocardiographie chez un emphysémateux de 43 ans au stade initial du cœur pulmonaire chronique P A P M 28 mm Hg Aspect filiforme des arteres pulmonaires à la peripherie Dans le lobe inferieur droit les arteres ne sont pratiquement pas injectées

La stenose des arteres lésees s observe dans neuf cas la reduction de la lumiere n excede jamais 50 % encore une telle réduction n interesse t elle qu un petit nombre de vaisseaux La proportion d arteres rétrecies ne depasse 30 % que dans deux cas (50 % et 80 %) Dans tous les cas cette stenose releve de l hyperplasie ou de la metaplasie musculaires

Les arteres d un calibre supérieur a 2 mm sont rarement indemnes les lesions habituellement non stenosantes consistent en un epaississement de l intima avec ou sans atherome Les capillaires ne sont pas alteres sauf un certain degre de dilatation

COMMENTAIRES

I — Mécanisme de l'hypertension artérielle pulmonaire

L'hypertension artérielle pulmonaire compliquant l'emphysème pulmonaire est une hypertension précapillaire elle relève donc nécessairement de



FIG 5 — Angiocardiographie chez un emphysemateux de 56 ans au stade d'insuffisance cardiaque droite réduite P A P M = 35 mm Hg Absence d'injection des artères pulmonaires à la périphérie des lobes

la [illegible]
c [illegible]
na [illegible]

a) FACTEURS ANATOMIQUES

[illegible]

proportion d'artères altérées était inférieure à 50 % Dans [illegible] contre cette proportion était égale ou supérieure à 50 %

Les confrontations entre données anatomiques et physiologiques (tableau IV) fournissent les renseignements suivants

— Sur 4 cas ou la pression artérielle pulmonaire mesurée au stade III était inférieure à 25 mm de mercure trois fois le pourcentage de petites arteres ou d artérioles lésées est inférieur à 30 %

— Dans 4 cas ou la pression arterielle pulmonaire mesurée au stade III est supérieure à 25 mm de mercure trois fois le pourcentage d arteres ou d artérioles lésées atteint ou dépasse 60 %

— Dans 4 cas enfin ou la pression artérielle pulmonaire mesurée au stade de l insuffisance cardiaque était supérieure à 45 le pourcentage d artères lésées atteint deux fois 70 % mais deux fois reste inférieur à 40 %

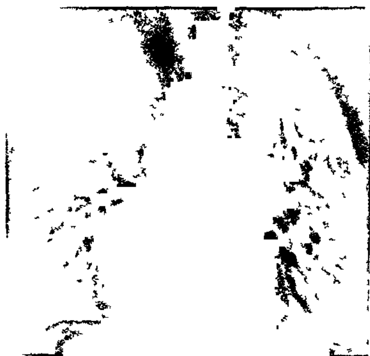


FIG 6 — *Angiocardiographie chez un emphysemateux de 52 ans* Cœur pulmonaire chronique réduit P A P M = 28 mm Hg Absence d injection des arteres pulmonaires périphériques sauf dans la partie moyenne des deux plages pulmonaires

Ces données quoique restreintes permettent cependant de conclure que le niveau de la pression artérielle pulmonaire une fois l insuffisance car diaque reduite dépend en partie de l extension des lésions pulmonaires C est a dire qu au stade III la pression artérielle pulmonaire reste relative ment élevée si les lésions anatomiques sont étendues Si ces lésions sont minimes la pression peut redevenir subnormale Au contraire au stade IV le niveau de l hypertension peut etre le meme pour deux malades dont

Tableau IV

Étude anatomique des petites artères et des artérioles dans douze cas de cœur pulmonaire chronique

	Petites artères de 2 mm à 100 µ						Artérioles < 100 µ						PAPM	État fonct
	Int	Méd	Adv	Thr	Sténose 1	Sténose 2	Int	Méd	Adv	Thr	Sténose 1	Sténose 2		
MAR	M 50	N	±	0	20	30	EL 90	0	N	0	0	0	18	IV DR
SYLV	M 20	N	N	+	20	20	N	0	N	0	0	0	22	IV DR
BIG	+ 5	+	N	0	0	0	N	0	N	0	0	0	22	IV DR
PALL	+ 20 °	N	N	0	20 °	20	+ 20	+ 20 °°	N	0	30 °	20 °	24	IV DR
PYR	N	+ 10	±	0	0	0	+ 10 °	+ 70 °	N	0	30 °	30	27	IV DR
GUIL	M 30	+ 30	N	0	30 %	30	+ 20 °	0	N	0	10	20 °	31	IV DR
LE F	N	+ 90	+	+	20	80	N	+ 80	+	0	0	0	37	IV DR
HAL	M 20 /	N	±	0	20 °	20	N	+ 60	N	0	20	50	43	IV DR
ROU	N	+ 30	N	++	20	30	N	+ 40	N	+	30 °	40	45	IV DF
RAF	M 70 °	+ 10	±	+	20	40	+ 75	+ 75 °	N	0	20	30	50	IV DF
GOR	M 30 °	+ 30 /	±	+	20	30	+ 30	0	N	0	10 °	30	52	IV DE
OUF	N	N	++ 70 /	±	0	0	N	0	+	0	0	0	57	IV DE

Int. = intima *Méd* = média *Adv* = adventice *Thr* = thromboses Sténos 1 = *degré de sténose de l'artère ou de l'artériole* Sténose 2 = pourcentage d'artères ou d'artérioles sténosées M* = *métaplasie musculaire dans l'intima* EL = présence de fibres élastiques dans l'intima artériolaire PAPM = Pression Artérielle Pulmonaire *Moyenne (en millimètres de mercure)* *État fonct* = État fonctionnel au moment de la mesure de pression

l extension des lésions varie du simple au double Ce fait suggere a ce stade le role predominant d un facteur surajoute

De telles notions conduisent a distinguer deux groupes anatomo cliniques

Pour l un de ces groupes les lésions anatomiques discretes n ont qu un role secondaire dans la genese de l hypertension arterielle pulmonaire Dans



FIG 7 — Ang ocard ograph e chez un emphysemateux de 53 ans au stade du cœur pulmona re chronique évolut f P A.P M = 43 mm Hg Mauva se inject on des artere pulmona res périphériques à gauche absence d inject on a dro te

l intervalle des poussees d insuffisance cardiaque les diverses constantes hemodynamiques tendent vers la normale Pour le deuxieme groupe l extension de l atteinte arterielle ou artériolaire semble commander en partie l évolution de la maladie en laissant persister dans l intervalle des crises des perturbations hemodynamiques importantes

Une telle distinction a eté établie par Cournand Pour cet auteur les deux formes evolutives tiennent a des differences a la fo s dans la structure des lesions et dans la maladie pulmonaire causale Or ici les lesions sont presque toutes du type musculaire il ne s agit de fibrose que dans un seul cas D autre part, ces deux formes anatomo cliniques ne se distinguent ni

par une plus grande durée d évolution ni par le plus grand âge des malades ni par des différences dans les perturbations fonctionnelles respiratoires En effet tous les malades étudiés dans ce travail ont une forte hypoxie lors les phases évolutives et les explorations fonctionnelles respiratoires fournissent des données identiques aussi bien pour les malades dont la pression reste



FIG 8 — Angiocardiographie chez un emphysemateux de 49 ans au stade du cœur pulmonaire chronique evolutif P A P M = 45 mm Hg Les artères pulmonaires peripheriques sont extrêmement greles et presque invisibles dans deux plages pulmonaires

modérement élevée que pour ceux dont la pression diminue fortement dans l intervalle des poussées

Le tableau V donne les valeurs moyennes et extremes obtenues pour certaines constantes respiratoires chez quinze malades de cette etude Un des malades ainsi exploré avait à l examen anatomique une hypertrophie de la media interessant 90 % des petites artères



Le mode d action des lésions anatomiques sur la circulation pulmonaire ne semble pas tenir à la reduction de la capacité du lit artériel En effet la réduction de la lumière des vaisseaux ne dépasse jamais 50 % et la proportion d artères sténosées n atteint 80 % que dans un cas Ainsi la réduc



Fig. 9. — Hypertrophie de la média d'une artère musculaire

Pas de sténose $\left(\text{Rapport } \frac{\text{paroi}}{\text{Diamètre artère}} = \frac{1}{5}\right)$

Homme de 42 ans P.A.P.M. = 46 mm de Hg au cours d'une insuffisance cardiaque évolutive

Fig. 10. — Épaississement de l'intima d'une artère. Métaplasie musculaire (fibres colorées en rouge par le trichrome de Masson)

Pas de sténose $\left(\text{Rapport } \frac{\text{paroi}}{\text{Diamètre artère}} = \frac{1}{7}\right)$

Homme de 53 ans P.A.P.M. = 18 mm Hg lors d'une phase régressive de l'insuffisance cardiaque



F G 11 — Les ons artér ola res

En haut arter ole legerement sténosée avec présence de cellules muscula res entre deux lim tantes élast ques

En bas chez le même su et l existe deux l m tantes elast ques (au l eu d une seule normalement) ma s les fibres musculaires sont absen es (concerne le même sujet que la figure 9)

tion totale du lit artériel atteint elle au maximum 30 % Une telle réduction du lit artériel pulmonaire est insuffisante à entraîner une hypertension artérielle (Haggart et Walker)

Ces lésions agissent surtout en diminuant la distensibilité des artères (Mounsey et collaborateurs) La réduction de distensibilité relève surtout de l hyperplasie ou de la métaplasie musculaire lésion très fréquente (11 fois

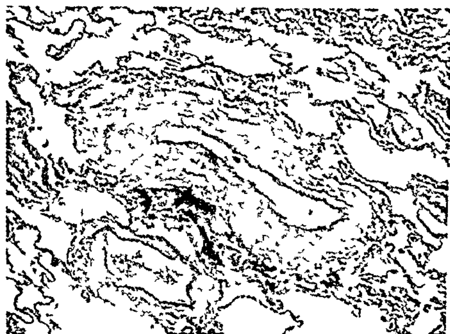


FIG 12 — Lésions adventitielles
Deux artères musculaires avec infiltration scléreuse de l adventice n entraînant pas de sténose 70 des artères sont intéressées L adventice des artérioles est pratiquement normal Homme de 51 ans P A P M = 57 mm Hg deux heures avant la mort

sur 12 dans cette série) et dont la constance a été déjà soulignée par Liebow et collaborateurs Le rôle de la sclérose adventitielle reste très secondaire sauf dans un seul cas où elle constitue l unique lésion

Ainsi l étude anatomique confrontée aux données physiologiques permet de retenir le rôle des lésions anatomiques dans l évolution du cœur pulmonaire Mais ce rôle est modeste et ne saurait expliquer les modalités évolutives des poussées du cœur pulmonaire chronique

TABLEAU V

Étude fonctionnelle respiratoire chez quinze malades avec cœur pulmonaire chronique par emphysème

	SUJETS NORMAUX (8)	C P C (15 SUJETS EXAMINÉS)	
		moyenne	extrêmes
Capacité vitale	4 620 cc	2 526	1 655 2 900
Volume résiduel	1 889 cc	2 988	2 100 4 300
Volume résiduel / Capacité totale	28	51 1	45 65
Capacité respiratoire maxima (l/mn)	135	33	18 59
C P U E / Capacité vitale	70	38 7	21 54

b) FACTEURS FONCTIONNELS

Le fait le plus remarquable apporté par les confrontations cliniques et *physiologiques est l amélioration de toutes les altérations hémodynamiques* lorsqu une insuffisance cardiaque est reduite par le traitement Le fait a éte souligné a plusieurs reprises (Mounsey et collaborateurs Cournand Harvey et collaborateurs) L étude du tableau I montre la réduction de l insaturation arterielle systemique de la pression arterielle pulmonaire (27 1 %) (fig 12) de [illegible] l index car di[illegible] %) [illegible] confronter globalement les valeurs moyennes obtenues pour l ensemble des malades de deux groupes on compare les données obtenues chez le meme patient explore a deux stades differents C est ce que montre le tableau VI etudiant les résul tats obtenus chez six patients explores successivement aux stades III et IV

TABLEAU VI

Donnees fournies par l exploration circulatoire chez six patients cathéterises successivement aux stades IV et III

	STADE I	STADE III	VARIATION
Sat Art Systém	60 8 /	8 9 /	+ 36 4 /
P A P M (mm Hg)	52	26	— 50 /
R A P (dyne /cm ⁵/sec	823	397	— 52

S t A t Systém = S tu t on oxygénée du ng rtéri l y témique
P A P M = P on Artér ll Pulm n re Moy nne
R A P = Ré t e Arté ll Pulm na e

Sur l ensemble de ces six cas le débit cardiaque augmente trois fois (30 3 % en moyenne) et diminue trois fois (31 % en moyenne) lors de la reduction de l insuffisance cardiaque Ainsi dans la moitié des cas seulement la diminution du débit cardiaque joue concurremment avec la chute de résistance artérielle pulmonaire pour déterminer la chute de pres

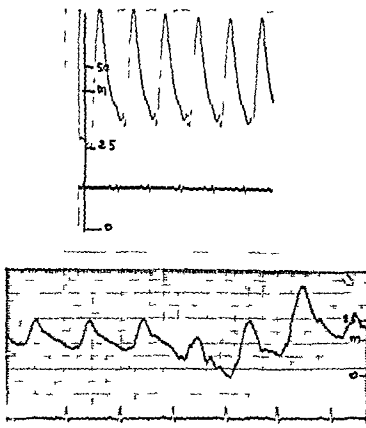


Fig 13 (a) — Malade explore successivement au stade de l insuffisance cardiaque évolutive (courbe du haut) et réduite (courbe du bas)

sion Dans les autres cas seule la chute des resistances joue puisque le débit cardiaque s eleve lors de la disparition des signes d insuffisance cardiaque

Cette notion d une diminution du débit cardiaque au stade de l insuffisance cardiaque parait en contradiction avec les donnees habituellement admises (Cournand Harvey McMichael) En realité de pareils faits ont eté signales par Fowler et collaborateurs qui trouvent généralement des index cardiaques bas Fishman et Richards admettent cette éventualite au stade terminal du cœur pulmonaire chronique il convient de souligner cependant que dans cette série les faibles débits cardiaques calculés au stade IV ne correspondent pas a une phase terminale de l évolution tous les malades ainsi explores survivent encore

L'accroissement de la capacité oxygénée (ou de l'hématocrite) a été considéré comme facteur adjuvant dans la genèse de l'hypertension artérielle pulmonaire. C'est en réalité un facteur inconstant car si pour l'ensemble des cas la capacité diminue du stade IV au stade III dans la série

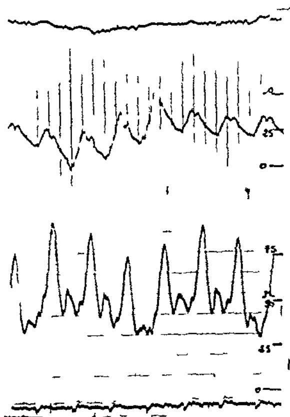


FIG. 13 (b). — Malade exploré successivement après la régression d'une poussée d'insuffisance cardiaque (courbe du haut) et au cours d'une seconde poussée (courbe du bas).

des six patients soumis à deux explorations successives la capacité varie diversement dans l'un ou l'autre sens.

Ainsi la confrontation clinico-physiologique au cours des poussées d'insuffisance cardiaque montre que dans la genèse de l'hypertension artérielle pulmonaire compliquant l'emphysème pulmonaire les élévations du volume globulaire et du débit cardiaque sont inconstantes ; ces facteurs sont contingents. Même lorsqu'ils existent ils sont insuffisants à rendre compte à eux seuls de l'hyperpression artérielle pulmonaire. Par contre l'accroissement de la résistance artérielle pulmonaire est un facteur constant, prédominant et souvent exclusif. Mais la réversibilité de cette augmentation de la

resistance affirme qu elle releve non de lésions anatomiques mais d une vaso constriction (Fishman et Richards)

Cette notion est confirmee par l action des hypotenseurs sur la pression arterielle pulmonaire Huit malades ont subi l injection d un vaso dépresseur (protoveratrine six cas hexaméthonium un cas hydralazine un cas) Les resultats sont resumés dans le tableau VII

La baisse de la pression arterielle pulmonaire est constante elle s associe a une forte diminution des résistances arterielles pulmonaires (— 30 %) plus importante que la chute de débit cardiaque d ailleurs inconstante

Ces résultats sont comparables a ceux obtenus par Fowler et collaborateurs utilisant le tétraéthylammonium Ils different de ceux rapportés par Sancetta avec l hexaméthonium Pour cet auteur les baisses de pression sont dues a la chute du debit cardiaque

TABLEAU VII

Action des vasodepresseurs dans huit cas de cœur pulmonaire chronique à différents stades

	CONTRÔLE	VASODÉPRESSEURS	VARIATIONS
P A P M (mm Hg)	27	16	— 41
I C (l/mn/m²)	3 22	2 83	— 12 2
R A P (dynes/cm⁻⁵ /s)	645	452	— 30

P A P M P ession artérielle pulmonaire moyenne
I C = Index cardiaque
R A P — Résistance artér elle pulmona re

Enfin [illegible]
et collabo [illegible]
forme de [illegible]
portion des lésions anatomiques stenosantes lorsqu elles existent Cet aspect filiforme est notable mais habituellement moins marque au stade initial du cœur pulmonaire chronique il semble etre moins accentue au stade III qu au stade IV

a) ROLES RESPECTIFS DES LESIONS ANATOMIQUES ET DE LA VASO CONSTRICTION

Les lésions anatomiques lorsqu elles atteignent plus de 50 % des arteres expliquent la persistance de l hypertension arterielle pulmonaire dans l intervalle des poussées Meme lorsqu elles n interessent qu une por [illegible] porte [illegible] sur [illegible] ation [illegible] tante [illegible] varie [illegible] l on observe chez les sujets normaux Ces faits semblent traduire une adaptation

insuffisante du lit artériel pulmonaire à un accroissement du debit (Fishman et Richards)

Le facteur anatomique ne joue qu un role secondaire dans la pathogénie *des poussées évolutives* *l élévation du debit cardiaque tres inconstante* ne dépasse pas au maximum 28 % et rend compte imparfaitement de l élévation de pression

La vaso-constriction arterielle ou artériolaire joue au contraire un role de premier plan dans le déterminisme des poussees évolutives (Fishman et Richards) si l on en juge sur l élévation de la résistance artérielle pulmo naire Elle intervient aussi au cours de certaines épreuves d effort dans 9 cas sur 21 la resistance artérielle pulmonaire s élève et dans 5 de ces 9 cas le débit cardiaque ne subit pas de variation De tels faits ont eté observes par Hickam et Cargill et par Riley et collaborateurs

La vaso constriction enfin joue un role certain au cours des crises d asthme La crise d asthme entraine constamment une hypertension pulmonaire meme dans les broncho pneumopathies bien tolérées Chez les malades en insuffisance cardiaque elle détermine un surcroit d hypertension (de 30 a *56, de 51 à 70 et de 50 à 80 mm de mercure respectivement dans trois cas)* Par contre, le debit cardiaque ne varie pas Il est donc évident que dans ces cas la vaso-constriction arteriolaire est seule en cause Les aérosols d amino phylline ramenent la pression artérielle pulmonaire a son niveau initial Buhr a obtenu des résultats semblables avec des aerosols d aleudrine

2 — Genèse de la vasoconstriction artérielle pulmonaire

Experimentalement Von Euler et Liljestrand chez l animal Motley et collaborateurs chez l homme ont montré que l inhalation de melanges gazeux pauvres en oxygene entraine une élévation de la pression arterielle pulmo naire La figure 14 montre que chez un meme patient toute elévation de la pression artérielle pulmonaire au cours de poussées évolutives s accompagne d une baisse de la saturation oxygénée du sang artériel systemique La figure 15 établie pour l ensemble des 102 malades de ce travail montre l exis [illegible]

faits semblables

Cependant l action de l oxygene sur la circulation pulmonaire fournit des resultats discordants en apparence en effet a tous les stades de l évolu tion l inhalation d oxygene pur entraine un accroissement de saturation oxy génée arterielle systémique ainsi qu une chute de pres sion artérielle pulmo naire d importance tres variable Par contre l action sur le débit cardiaque et les resistances varie suivant le stade évolutif (tableau III) Au stade initial du cœur pulmonaire chronique les résistances arterielles pulmonaires dimi nuent fortement sans variation appréciable du debit cardiaque au stade de l insuffisance cardiaque débit et resistances diminuent parallelement au stade de l insuffisance cardiaque évolutive le debit cardiaque subit une dimi *nution nette (— 31 4 %) alors que les resistances s élèvent Wilson et* collaborateurs ont obtenu des résultats comparables

Ces faits ainsi que la constatation de larges variations individuelles (fig 15) en l absence de differences anatomiques significatives suggerent

qu un autre processus peut s associer à l anoxie dans le determinisme de

admettent le role aggravant de la retention de CO₂ sur l hypertension arté rielle pulmonaire Expérimentalement d ailleurs l hypercapnie détermine une hypertension arterielle pulmonaire (Duke Von Euler et Liljestrand) Une telle hypothese expliquerait les résultats fournis par l inhalation d oxy

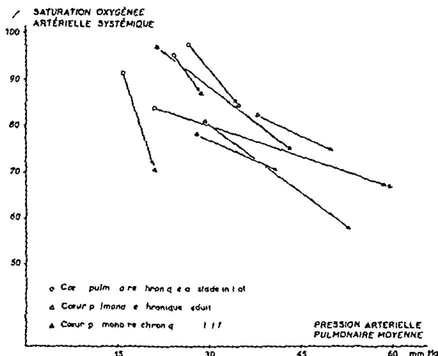


FIG 14 — *Confrontations entre la pression arterielle pulmonaire et la saturation oxygenee du sang artériel systémique chez 8 malades observes a deux stades differents de leur cœur pulmonaire chronique*

gene Au stade initial du cœur pulmonaire chronique la retention de CO2 est minime la correction de l hypoxie n aggrave pas cette retention et entraine la diminution des résistances Au stade de l insuffisance cardiaque evolutive au contraire la retention de CO2 est majeure La correction de l hypoxie reduit la ventilation et accroit l hypercapnie (Taquini Mounsey et collaborateurs) De ce fait la vaso constriction persiste Dans ces conditions la baisse de pression arterielle pulmonaire releve exclusivement de la diminution du debit cardiaque

Que l hypoxie determine la vaso constriction isolément ou associée a

ganglion cervical moyen supprime l hypertension arterielle pulmonaire

déclenchée par l'anoxie chez le chien. Peters et Roos ont montré d'autre part l'accroissement unilatéral de résistance lorsqu'un des deux poumons est ventilé avec de l'azote. Il est possible que ces réflexes vaso-constricteurs sollicités par les variations pathologiques de la fonction respiratoire (asthme, surinfection) ou par l'effort constituent le stimulus de l'hyperplasie ou de la métaplasie musculaire. Ainsi s'expliquerait la genèse des lésions les plus fréquemment rencontrées. Par contre la sclérose adventitielle ne saurait répondre à une telle pathogénie. Elle semble être la conséquence de lésions inflammatoires liées à l'évolution de l'infection broncho-pulmonaire.

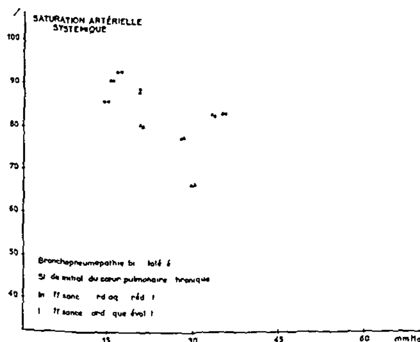


FIG. 15. — Confrontations entre la saturation oxygénée du sang artériel systémique et la valeur de la pression artérielle pulmonaire moyenne chez 95 malades atteints de maladie broncho-pulmonaire chronique.

RÉSUMÉ

D'une étude physiologique portant sur 102 malades atteints d'emphysème avec ou sans asthme et de l'étude anatomique faite chez douze de ces malades on peut tirer les conclusions suivantes :

L'hypertension artérielle pulmonaire relève primitivement dans la plupart des cas de l'hypoxie associée ou non à l'hypercapnie. Cette hypoxie détermine une vaso-constriction réflexe des petites artères et des artérioles pulmonaires. La répétition de cette vaso-constriction finit par entraîner une hyperplasie ou une métaplasie musculaire. Dès lors l'évolution de l'hypertension artérielle pulmonaire dépend de deux facteurs :

— la vaso constriction liée à l anoxie et par conséquent en rapport avec le degré d emphysème

— l extension des lésions artérielles pulmonaires

Lorsque les lesions anatomiques sont rares et discretes l'évolution est fonction des poussées de la maladie broncho pulmonaire Si ces poussées sont totalement réductibles la pression artérielle pulmonaire reprend dans les phases intercalaires une valeur sensiblement normale Dans le cas contraire une hypertension d un degré variable persiste entre les poussees

Lorsque les lésions anatomiques presque toujours musculaires (11 fois [illegible] poussées d hypertension [illegible] Mais dans les phases [illegible] elevee malgre la correction de l hypoxie du fait de la reduction de distensibilité des arteres pulmonaires

SUMMARY

The physiological study of 102 patients suffering from emphysema with or without chronic asthma as well as anatomical investigation of 12 cases, enable us to draw the following conclusions

Pulmonary arterial hypertension originally depends in almost all cases on hypoxia associated or not with hypercapnia

Hypoxia brings about a vasoconstrictor reflex of the pulmonary small arteries and arterioles

The recurrence of this vasoconstriction finally causes hyperplasia or muscular metaplasia From then on pulmonary arterial hypertension depends on two factors

— vasoconstriction linked to anoxia and therefore dependant on the degree of emphysema

— the extent of the damage done to pulmonary arterioles

When the anatomical lesions are few and slight the development is related to the paroxyms of the broncho pulmonary disease

When paroxysms are totally reducible pulmonary arterial pressure almost returns to normal during intermediate states Otherwise hyper tension of variable degree persists between the paroxysms

When the anatomical lesions almost always muscular affect a large percentage of the arteries paroxysms of pulmonary arterial hypertension remain dependant on the degree of hypoxia But during intervals arterial pressure remains moderately high despite the effect of hypoxia on account of the diminished distensibility of pulmonary arteries

ZUSAMMENFASSUNG

Physiologische Studien an 102 an Emphysem leidenden Patienten mit oder ohne Asthma sowie anatomische Erforschung von 12 Fallen erlauben uns folgende Schlusse zu ziehen

Arterielle pulmonare Hypertonie hängt ursprünglich fast in allen Fällen von Hypoxie ab die mit Hyperkapnie vergesellschaftet sein kann

Hypoxie verursacht einen vaso konstriktorischen Reflex der kleinen Lungenarterien und arteriolen

Die Wiederholung dieser Vasokonstriktion bringt schliesslich Hyperplasie oder muskuläre Metaplasie mit sich Von da an hängt die arterielle pulmonare Hypertonie von 2 Faktoren ab

— Mit Anoxie verbundener Vasokonstriktion und daher vom Grad des Emphysems

— dem Ausmass des Schadens an den Lungenarteriolen

Wenn anatomische Läsionen selten und nur leicht sind hängt die Entwicklung mit den Anfällen der broncho pulmonaren Erkrankung zusammen

Wenn es gelingt die Anfälle völlig zu kupieren kehrt der pulmonare Arteriendruck in den anfallsfreien Perioden zur Norm zurück Anderenfalls bleibt Hypertonie von variabler Höhe zwischen den Anfällen bestehen

Wenn die anatomischen zum Grossteil muskulären Läsionen einen grossen Prozentsatz der Arterien befallen haben bleiben die Anfälle arterieller pulmonarer Hypertonie vom Grad der Hypoxie abhängig Aber während der Intervalle bleibt der Arteriendruck mässig hoch trots der Hypoxieschutzvorrichtung wegen der verminderten Ausdehnbarkeit der Lungenarterien

RESUMEN

El estudio fisiológico de 102 pacientes de enfisema con o sin asma y *el estudio anatómico realizado en 12 de estos enfermos permite deducir* las siguientes conclusiones

La hipertensión arterial pulmonar indica en la mayoría de los casos la existencia de una hipoxia asociada o no a hipercapnia Esta hipoxia determina una vasoconstricción *refleja de las pequeñas arterias y arteriolas pulmonares* La repetición de esta vasoconstricción termina por producir una hiperplasia o una metaplasia musculares Desde ese momento la evolución de la hipertensión arterial pulmonar depende de dos factores

— *la vasoconstricción vinculada a la anoxia y por consiguiente en relación con el grado de enfisema*

— la importancia de las lesiones arteriales pulmonares

Cuando las lesiones anatómicas son raras y reducidas la evolución es *función de las recidivas de la enfermedad* broncopulmonar Si estas recidivas son totalmente reducibles la presión arterial pulmonar vuelve a su

' En caso contrario persiste una hiper

casi siempre musculares (11 casos sobre 12) interesan a un elevado porcentaje de arterias los episodios de hipertensión arterial continúan vinculados al grado de hipoxia pero en las fases intermedias la presión arterial se mantiene moderadamente elevada no obstante la corrección de la hipoxia debido a la menor distensibilidad de las arterias pulmonares

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MODIFICATIONS CIRCULATOIRES CONSÉCUTIVES AUX ÉTATS D'ANOXÉMIE CLINIQUES ET EXPÉRIMENTAUX

par

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Von Euler et Liljestrand ont montré en 1946 que l'on pouvait observer une élévation de la pression artérielle pulmonaire chez les chats à qui l'on faisait respirer une atmosphère pauvre en oxygène. Motley, Cournand et coll. (1947) devaient confirmer ces constatations chez l'homme. Par ailleurs on sait que la pression artérielle pulmonaire est plus élevée chez les sujets vivant aux hautes altitudes que chez ceux habitant au niveau de la mer. En règle habituelle l'hypertension artérielle rencontrée dans des conditions pathologiques ou expérimentales s'accompagnant d'anoxémie est d'autant plus importante que la désaturation oxygénée du sang artériel est considérable (fig. 1). *Les mécanismes par lesquels l'anoxémie élève la pression artérielle pulmonaire ont fait l'objet de nombreuses recherches mais restent encore conjecturaux.* Fishman et coll. (1952) ont pu démontrer que l'anoxémie entraînait un accroissement significatif du débit cardiaque ; celui-ci est toutefois insuffisant pour rendre compte à lui seul de l'hypertension pulmonaire observée. Une augmentation éventuelle de la masse sanguine intra-pulmonaire a parfois été invoquée pour expliquer cette hypertension ; les techniques utilisées pour une telle détermination restent assez peu précises et ont donné des résultats contradictoires. Salonikidès (1958) a noté un accroissement

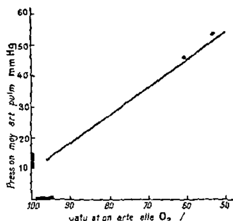


FIG. 1. — Influence de l'anoxémie sur la pression artérielle pulmonaire.

tres net du volume sanguin central dans des etats s'accompagnant d'une hypoxemie arterielle accentuee pour Cournand (1957) par contre les variations mises en evidence dans des conditions similaires ne sont pas significatives Une observation pleine d'interet a ete faite par Cournand l'effet de l'anoxemie sur la pression arterielle pulmonaire reste le meme avant et apres sympathectomie bilaterale etendue ce fait fut demontré chez un patient porteur d'une maladie de Raynaud et soumis à l'intervention chirurgicale il apparait par consequent que l'effet hypertenseur de l'hypoxie est independant du systeme sympathique On a parfois emis l'hypothèse que l'hypoxie agirait par un reflexe alveolo vasculaire n'empruntant pas le systeme autonome et produisant un accroissement des resistances vasculaires pulmonaires s'appuyant sur des experiences tres ingenieuse Cournand a pu rejeter d'une façon decisive cette façon de voir (1955) De recentes recherches poursuivies par l'Ecole de Cournand sont particulièrement penétrantes et ont permis une approche nouvelle de ce problème l'infusion intra arterielle pulmonaire d'acetylcholine provoque une chute significative des pressions prealablement elevees par l'hypoxie ceci s'observe sans modifications nouvelles du debit cardiaque accru par l'hypoxie ou de la pression capillaire pulmonaire de plus on ne note aucune variation de la pression artérielle periphérique etant donne la rapide inactivation de l'acetylcholine par la cholinestérase Le segment vasculaire sur lequel agit l'acetylcholine reste inconnu Ces constatations sont d'un grand interet elles montrent 1° que des substances prenant naissance dans le sang peuvent agir directement sur la paroi d'un segment encore imprecise de l'appareil vasculaire pulmonaire 2° que les effets de l'hypoxie qui determinent à la fois un accroissement du débit pulmonaire et une vaso constriction peuvent etre nettement dissocies 3° que la vasoconstriction associee a l'hypoxie est reversible

En pathologie humaine il existe deux types de pneumopathies s'accompagnant d'anoxemie ces deux formes peuvent exister à l'etat pur assez souvent elles sont intriquées a) *pneumopathies caracterisees par de l'hypoventilation alveolaire* b) *pneumopathies s'accompagnant de troubles de la diffusion des gaz au niveau de la membrane alvéolo capillaire*

a) Les pneumopathies avec hypoventilation alveolaire sont essentiellement realisees par des etats importants d'emphyseme pulmonaire la diminution de la pression partielle d'oxygene et l'augmentation de la pression partielle d'anhydride carbonique dans les alveoles entrainent de l'anoxemie et de l'hypercapnie L'anoxemie a diverses consequences dont la plus significative est l'hypertension pulmonaire dont nous avons parlé precedemment Par ailleurs par suite du stimulus anoxique la masse sanguine globulaire

De telles modifications hémodynamiques (augmentation du debit cardiaque des pressions pulmonaires de la masse sanguine) par l'accroissement du travail ventriculaire droit qu'elles entrainent provoquent a plus ou moins longue echéance de l'hypertrophie du cœur droit avec image de surcharge ventriculaire droite a l'electrocardiogramme et finalement de l'insuffisance cardiaque droite l'insuffisance myocardique ainsi réalisee est assez particuliere puisque contrairement aux formes classiques d'insuffisance cardia-

que elle peut s accompagner d un débit du cœur pouvant rester superieur a la normale (fig 2) Il n y a cependant pas de difference essentielle entre ce type d insuffisance cardiaque et les autres car en fait ici aussi bien que paraissant eleve le débit du cœur est insuffisant pour les besoins metaboliques du patient Dans ces pneumopathies l anoxémie constitue le facteur

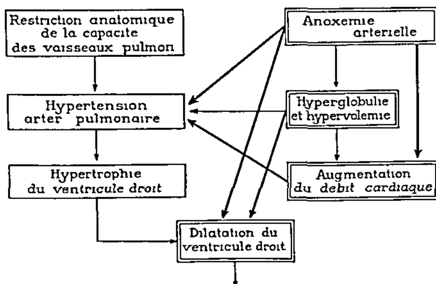


Fig 2 — Facteurs déterminant l insuffisance cardiaque dans l emphyseme avec anoxémie

essentiel de l apparition du cœur pulmonaire chronique les lesions vasculaires pulmonaires qui sont plus ou moins importantes selon les cas paraissent ne jouer qu un role secondaire

b) Cournand et ses collaborateurs ont decrit en 1951 un syndrome particulier qu ils ont appelé *bloc alvéolo capillaire* Il s agit de pneumopathies au cours desquelles on observe des troubles de la diffusion des gaz au niveau de la paroi alvéolaire ces conditions sont réalisees notamment par les granulomes pulmonaires dus au beryllium par le sarcoide de Boeck par certaines fibroses pulmonaires (sclérodermie asbestose) au cours de la carcinomatose miliaire du poumon enfin dans la tuberculose *hematogene pulmonaire lors* de sa phase aigue Chez ces malades les examens anatomo pathologiques montrent un envahissement ou un épaississement des septa alveolo capillaires Ces derniers peuvent etre occupés par du tissu fibreux granulomateux parfois tuberculeux ou carcinomateux selon les cas

Chez beaucoup de ces patients le début de la maladie est insidieux et est marque par de la dyspnée et de la tachypnée survenant tout d abord lors de l exercice puis persistant au repos La cyanose est habituellement moderée mais s accentue considérablement à l effort Les examens physiologiques montrent une tension alveolaire en oxygene elevee un accroissement marqué

du gradient alveole sang arteriel en oxygene une desaturation oxygenee arterielle faible au repos mais augmentant lors de l effort une hypertension artérielle pulmonaire moderee ou importante selon les cas un debit cardiaque genéralement accru Ces malades evoluent comme les patients atteints d emphyseme et finissent pour les memes raisons par presenter de l insuffisance cardiaque ils meurent assez frequemment cependant avant que celle ci n ait eu le temps de s installer

Il est interessant d opposer ces etats cliniques et experimentaux ou l anoxemie domine la scene a ceux caracterises essentiellement par une *reduction du lit vasculaire pulmonaire* Experimentalement on a pu demontrer

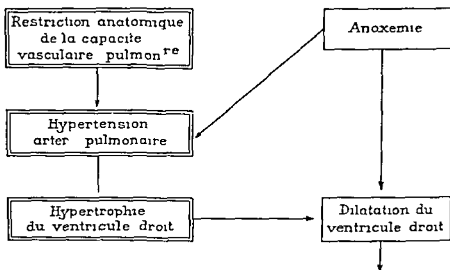


FIG 3 — Facteurs determinant l insuffisance cardiaque dans les pneumopathies avec reduction du lit vasculaire

que des reductions localisees du lit vasculaire pulmonaire ne produisent pas d hypertension arterielle pulmonaire c est ainsi qu apres pneumonectomie alors que le debit cardiaque est cependant double la pression pulmonaire reste generalement normale ou sensiblement normale (Denolin 1955) Pour que la pression arterielle pulmonaire s eleve il est necessaire que la vascularisation pulmonaire soit reduite d une façon généralisée c est ce qui a éte montré d une façon tres suggestive par Courtoy et Salonikides (1956) lorsque l on realise une obstruction diffuse de la circulation pulmonaire par injections repetees de spores de lycopode dans le tronc commun de l artere pulmonaire on observe une hypertension pulmonaire precoce et importante due essentiellement au blocage mecanique des arterioles pulmonaires

En pathologie humaine une restriction generalisee de la capacite vasculaire des poumons peut etre rencontree dans des maladies tres diverses *embolies pulmonaires recurrentes anemie drepanocytaire* (sickle cell anemia) qui provoque une thrombose occlusive des petites arteres pulmonaires *schistosomiase,* frequente en Égypte *thromboses pulmonaires artérites pulmo*

naires variées (periartérite noueuse, lupus érythémateux), *hypertension artérielle primitive* : cette dernière condition clinique, qui peut exister à l'état isolé ou accompagner certaines cardiopathies congénitales, paraît résulter de la persistance après la naissance d'une circulation pulmonaire du type fœtal.

L'hypertension pulmonaire observée dans ces différentes maladies est variable : minime et évoluant lentement ou importante et rapidement progressive, elle subit des à-coups constants provoqués par toute augmentation du débit cardiaque sous l'influence d'efforts quotidiens répétés ou d'infections. Elle entraîne une hypertrophie du cœur droit et à plus ou moins brève échéance de l'insuffisance cardiaque droite. Cette insuffisance cardiaque, contrairement à celle rencontrée dans les états où l'anoxémie joue le rôle principal, s'accompagne d'un débit du cœur diminué (fig. 3). Son apparition est cependant assez souvent hâtée par une poussée d'anoxémie aiguë consécutive à une infection broncho-pulmonaire.

RÉSUMÉ

L'anoxémie expérimentale détermine chez l'homme ou chez l'animal d'expérience diverses modifications de la dynamique circulatoire : accroissement du débit cardiaque, élévation des pressions artérielles pulmonaires, augmentation de la masse sanguine. Les mécanismes en cause sont analysés : les variations du volume minute résultent essentiellement de l'action de l'anoxémie sur le myocarde ; l'hypertension artérielle pulmonaire ne paraît pas due à l'augmentation du débit cardiaque ou à d'éventuelles modifications du volume sanguin intra-thoracique ; ces facteurs n'ont tout au plus qu'un rôle accessoire ; l'élévation de la pression pulmonaire est indépendante du système nerveux ; les expériences les plus récentes semblent indiquer qu'elle est provoquée par une action directe de l'anoxémie sur un segment encore imprécisé de l'appareil vasculaire pulmonaire. En pathologie humaine il existe deux types de pneumopathies s'accompagnant d'anoxémie ; ces deux formes peuvent exister à l'état pur ; assez souvent elles sont intriquées : 1°) pneumopathies caractérisées par de l'hypoventilation alvéolaire ; 2°) pneumopathies s'accompagnant de troubles de la diffusion des gaz au niveau de la membrane alvéolo-capillaire. Au cours de ces conditions cliniques on observe un accroissement du travail ventriculaire droit responsable de l'hypertrophie du cœur droit et finalement d'une insuffisance cardiaque droite à débit du cœur élevé. Il n'y a cependant pas de différence essentielle entre ce type d'insuffisance cardiaque et les formes classiques, car ici aussi bien que paraissant élevé le débit du cœur est insuffisant pour les besoins métaboliques du patient.

Les états cliniques et expérimentaux où l'anoxémie domine la scène sont confrontés avec ceux caractérisés avant tout par une réduction du lit vasculaire pulmonaire.

SUMMARY

Experimental anoxaemia causes in man and laboratory animals various alterations of the dynamics of circulation increase of the cardiac flow rise of pulmonary arterial pressure increase of the volume of the blood *The involved mechanisms have been studied Fluctuations of the volume* per minute are chiefly caused by the action of anoxaemia on the myocardium arterial pulmonary hypertension does not seem to result from a possible increase of the cardiac flow nor from eventual alterations of blood volume in the thorax

These factors can at the most play an accessory part The rise of pulmonary pressure is independant of the nervous system Our latest experiments seem to indicate that its causes are the direct action of anoxaemia on a yet undertermined section of the pulmonary vasculature

In human pathology there are two types of pneumonopathies which are associated with anoxaemia They may appear either in a pure or involved form

1° Pneumonopathies characterized by alveolar hypoventilation

2° Pneumonopathies with disturbances of the diffusion of gases at the level of the alveolar capillary membrane

Under such conditions increased work of the right ventricle of the heart is responsible for the hypertrophy of the right heart and bringing on finally cardiac insufficiency with a high cardiac flow However no essential differences between this type of cardiac insufficiency and classical ones can be found In all cases despite its seemingly large volume the cardiac flow is unable to meet with the patients metabolic requirements

Clinical and experimental cases in which anoxaemia plays the leading part are contrasted and compared with cases whose main features are a reduction of the pulmonary vascular bed

ZUSAMMENFASSUNG

Die experimentelle Anoxamie bedingt beim Menschen oder dem Tier erfahrungsgemass verschiedene Modifikationen der Dunamik des Kreislaufes Anstieg des Herzminutenvolumen Erhohung des Druckes der Lungenarterien Anwachsen der Blutmenge Die dies verursachenden [illegible] utenvolumens resultie[illegible] auf den *Herzmuskel* [illegible] durch ein Vergrosserung des Minutenvolumens des Herzens oder eventuelle Modifikationen des Blutvolumens in dem Thorax bedingt zu sein Diese Faktoren spielen hochstens eine nebensachliche Rolle Die Erhohung des Druckes in der Lunge ist von dem Nervensystem abhangig Die jungsten Erfahrungen schienen zu zeigen dass sie durch eine direkte Aktion der Anoxamie auf einen noch nicht bestimmten Teil des Gefasspparates der Lunge hervorgerufen wird In der menschlichen Pathologie gibt es zwei Arten von Pneu

mopathien die die Anoxämie begleiten Diese beiden Formen können rein vorkommen meist aber treten sie zusammen auf

1° durch alveolare Hypoventilation gekennzeichnete Pneumopathien

2° Pneumopathien welche von Störungen in der Verteilung von den Gasen auf dem Niveau der alveol kapillären Membranen begleitet sind Im Zuge dieser klinischen Zustände bemerkt man rechts ein Anwachsen der ventrikulären Arbeit welche für die Hypertrophie des rechten Herzens und schliesslich eine Unzulänglichkeit des rechten Herzens bei erhöhtem Minutenvolumens verantwortlich ist Folglich gibt es keinen prinzipiellen Unterschied zwischen diesem Typ der Herzinsuffisiens und den klassischen Formen denn auch hier ist das Minutenvolumens obwohl es erhöht scheint unzureichend für die Bedürfnisse des Stoffwechsels des Patienten Die klinischen und experimentellen Zustände in welchen die Anoxämie das Bild beherrschstehen jenen gegenüber die vor allem durch eine Reduktion des Gefässbettes der Lunge charakterisiert sind

RESUMEN

La anoxemia experimental en el hombre o en los animales de experimentacion produce diversas modificaciones de la dinámica circulatoria aumento del caudal cardiaco elevacion de la presión arterial pulmonar aumento de la masa sanguinea Del analisis de los mecanismos cau antes resulta que las variaciones del caudal son debidas esencialmente a la acción de la anoxemia sobre el miocardio que la hipertensión arterial pulmonar no parece ser causada por el aumento del caudal cardíaco o por eventuales modificaciones del volumen sanguíneo factores que desempeñan un papel accesorio que la elevación de la presion pulmonar es independiente del sistema nervioso y que es producida por una acción directa de la anoxemia sobre un segmento aun no definido del aparato vascular pulmonar segun parecen indicar las experiencias más recientes

En patologia humana existen dos tipos de neumopatias que acompañan a la anoxemia a menudo simultaneamente aunque pueden existir puros 1° neumopatias caracterizadas por la hipoventilación alveolar 2° neumopatías acompanadas por trastornos de la difusión gaseosa al nivel de la membrana alveolo capilar En estas condiciones clinicas se observa un aumento del trabajo ventricular derecho responsable de la hipertrofia del corazon derecho y finalmente de una insuficiencia cardíaca derecha con caudal del corazón elevado Sin embargo no hay una diferencia esencial entre este tupo de insuficiencia cardíaca y las formas clásicas pues aquí tambien aunque el caudal es elevado resulta insuficiente para las necesidades metabólicas del paciente

Se comparan los estados clinicos y experimentales en los que la anoxemia domina el cuadro con aquellos caracterizados sobre todo por una reducción del lecho vascular pulmonar

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ZUR PATHOGENESE DES EMPHYSEMS

von

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Das Emphysem teilt das Schicksal anderer Erkrankungen des Respirations-Apparates von einer Krankheitseinheit zum *Symptomen-Komplex* geworden zu sein. Dies bedeutet im Grunde nichts anderes als die schon lang bekannte Tatsache, dass verschiedene, ja viele Wege zum Emphysem führen. Hier soll vor allen von der oder den Formen des Emphysems die Rede sein, die *Komplikationen* anderer Lungen-Affektionen sind, und zwar um *die* Formen [illegible] kutiver distaler Ueber[illegible] Sie können zum ech[illegible] relativ häufigen Mechanismus.

Mit Sicherheit handelt es sich bei den emphysematischen Zuständen um Veränderungen im eigentlichen *respiratorischen Parenchym*, wobei beide Auffassungen der Lungenstruktur, die des segmentaren Baues wie die der Unterscheidung in Lungen*kern* (Stiehl) und Lungen*mantel* für die Emphysem-Genese in gleicher Weise in Betracht kommen. Emphysem bedeutet vorläufigen Endpunkt einer pathologischen Entwicklung.

Es erscheint zweckmässig, das *Symbol* Emphysem beizubehalten. Dieser Ausdruck praejudiziert nichts bezüglich Genese wie etwa der „chronisch obstruktiven Lungen-Atrophie", der wohl etwas enger gefasst ist, aber z.B. den Bedingungen gewissen Formen wie etwa der des senilen Emphysems nicht gerecht wird.

Ueber die Begriffe muss man sich aber einigen, um nicht aneinander vorbeizureden.

Allgemein versteht man unter Emphysem den chronischen weitgehend irreversiblen Zustand des Lungenparenchyms, das Volumen pulmonum auctum chronicum, das dem reversiblen Volumen pulm. auct. acutum der Lungenblähung gegenüber gestellt werden kann.

Emphysematöse Zustände gehen durch die ganze Lungen-Pathologie hindurch, bilden die häufigsten pathologischen Lungenveränderungen überhaupt und beherrschen dadurch weite Gebiete der Lungenaffektionen.

Emphysem und Atelektase sind in vielen Punkten genetisch nahe verwandt, besonders die Obstruktionsatelektase, bei *völliger* Unterbrechung des Luftstromes eintretend, während zur Entstehung des Emphysems zum

mindesten der inspiratorische Weg noch offen stehen muss Im Gegensatz aber zur Atelektase tritt Emphysem klinisch viel haufiger auch als *selbstandige Krankheit* in Erscheinung

Alle Emphysem Formen werden mit der Zeit Ruckwirkungen auf den kleinen Kreislauf zur Folge haben die bald fruher bald spater als Cor pulmonale in Erscheinung treten Dieses stellt einen Kompensations mechanismus dar von seiten des weitgehend anpassungsfahigen Herzens auf gelast durch erhohter Druck in der Arterie pulmonchis der wenn die Grenzen dieser Anpassung uberschritten werden zur Dekompensation und damit zu schweren Zirkulationsstorungen zunachst im kleinen Kreislauf fuhrt

Alle verengten Wege im Broncho pulmonalen Ventilations System konnen zu Emphysem 'urch welche Momente die der *Ort* derselben vor alle allen ausschlaggebend die *Dauer* der Verengerung Die Ursachen bestreichen also ein weites Feld das von der rein psychogenen Behinderung der Luft wege bis zu grob mechanischen reicht Dabei ist besonders zu beachten dass gerade die durch zahlreiche Herde (Miliar Tuberkulose Miliar Boeck sche Erkrankung Silikose) und deren Schrumpfung erzeugten multizentri schen Emphysem Entwicklungen besonders hohe Grade erreichen konnen doch kommen diese fur die hier interessierende Emphysem Genese weniger in Betracht

Unter den Ursachen die von Gesichtspunkten der Allergie Lehre aus in Frage kommen steht das *Asthma* an erster Stelle Fur das Asthma gilt dasselbe wie fur das Emphysem Es ist ebenfalls von einer Kran kheitseinheit zu einem Syndrom geworden Syndrom seinerseits auch wieder sehr verschiedener Genese doch stehen hier primar funktionelle und allergische Momente stark im Vordergrund neben entreindeichen primaren oder consekutiven

Da allergische Zustande sowohl die Schleimhaut und deren Sekretion beeinflussen als auch uber das Nervensystem die Muskulatur der feinern Luftwege beherrschen konnen allergische Zustande von beiden Angriff sorten aus durch Verengerung der Luftstrombahnen zum Emphysem fuhren Es ist dann fur diese Verengerung nicht mehr ausschlaggebend wo der primare Angriffspunkt liegt sondern nur noch der Umstand dass uberhaupt die Verengerung zustande gekommen ist *und dauert* Es ist gleichgultig ob dieselbe immer wieder durch Allergene hervorgerufen wird oder ob eine psychische Fixation des Mechanismus erfolgt ist (beding ter Reflex) denn in ihrem Endeffekt wirken beide Zustande im Sinne der Erschwerung der Expiration damit im Sinne der immer wiederkehrenden Lungenblahung die schliesslich permanenten Dehnung und zum alveolaren Substanzverlust fuhrt und damit zu schwerer Einengung der pulmonalen Strombahn

Dass Asthma auch experimentell nach dem Mechanismus der bedingten Reflexe im Tierversuch auslosbar ist haben unsere Mitarbeiter gezeigt Wird einem Meerschweinchen zusammen mit dem Erklingen eines bestimmten Tones ein Reizstoff appliziert der Asthma auslost so kann in der Folgezeit durch den *Ton allein* der Asthma Anfall ausgelost werden nach dem Mechanismus eines bedingten Reflexes

Die Ausbildung des Emphysems setzt jahrelanges Bestehen des Asthmas voraus So wird denn auch in der überwiegenden Mehrzahl der chronischen Asthma Fälle ausgesprochen diffuses Emphysem gefunden

Betrachten wir die Situation von Seiten des Emphysems her so finden sich in rund einem Sechstel der Fälle Asthma (*Abott* und Mitarbeiter) Die Dauer des Asthmas bis zur Ausbildung ausgesprochenen Emphysems wird auf mindestens 3 Jahre veranschlagt Doch sind auch kürzere Zeiten beobachtet worden Dabei ist zu berücksichtigen dass Asthma und Asthma sehr verschiedene Intensitätsgrade aufweisen können Beim kindlichen Asthma finden wir im Gegensatz zu dem länger dauernden des Erwach senen nur relativ geringfügige Emphysem Befunde Bei Asthma Todes fällen des Erwachsenen (Geiser) besteht zwar meist hochgradiges Lungen emphysem doch überwiegen der Verschluss der Bronchien und Bronchio len durch Schleim Pfropfen Andererseits sind aber auch langdauernde Asthma Zustände bekannt die ohne Emphysem Bildung verlaufen sind Auch fanden *Thiene* und Sheldon unter 10 Asthmatikern (18 70 Jahre) bei denen Asthma 8 40 Jahre bestanden hatte 2 Fälle *ohne* Lungenveran derungen woraus sie schliessen dass Asthma bestehen kann ohne Dauer veränderung im Lungenparenchym hervorzurufen

Wichtiger noch für das klinisch etikettierte Asthma scheinen *chronische bronchospastische Zustände zu sein* Ueber Vorkommen und Häufigkeit chronischer Bronchitis bestehen in den verschiedenen Ländern sehr weit auseinandergehende Auffassungen Differenzen die sich kaum allein auf solche des Klimas beziehen sondern wohl auch solche der pathogenetischen Betrachtungsweise sind So wäre in England die chronische Bronchitis mehr als 10 × so häufig wie z Bl in der Schweiz

Besondere Aufmerksamkeit sollte in dieser Beziehung der sogn *eosino philen Bronchitis* oder dem *eosinophilen Katarrh (Schwenkenbecher)* schenkt werden Es handelt sich um ein relativ wenig beachtetes Krankheitsbild das dem Asthma verwandt ist aber keineswegs zu Asthma zu führen braucht oder eigentliche asthmatische Episoden aufzu weisenbrancht Dabei ist auffallend und in der Richtung allergischen Geschehens weisend die ausgesprochene Eosinophilie des Sputums (und des Blutes) während die spastische Komponente klinisch durch bronchiales Giemen *manifest* wird

Dass dem typischen Emphysem häufig chronische Katarrhe voran gehen ist neuerdings wieder von *Christie* hervorgehaben worden Dabei liegt aber der Hauptakzent auf den Bronchospastischen Zustände (Volhard Hadorn Wyss u a)

Die Wichtigkeit chronischer Exspirationsbehinderung und damit auch das Asthma Intervall kann nicht genug hervorgehoben werden Der grosse Asthma Anfall beherrscht die Szene und wenn er spontan oder medika mentös abgeklungen ist fühlt sich der Kranke in der Regel derart erleich tert dass er eine weitere Therapie für unnütz hält und sich häufig ärztlicher Beobachtung entzieht bis wieder ein grosser Anfall eintritt Der Kranke findet sich häufig ab mit einer subjektiv tolerablen Durchgängigkeit der Respirationswege Im Gegensatz nun zum Anfall dauert aber diese relative Behinderung der Exspiration nicht nur Tage sondern Monate unter Um standen Jahre und Jahrzehnte oft gelegentlich nur unterbrochen durch schwerere Anfälle die ärztliche Intervention erheischen Durch die lange

Dauer wird daher die *Behinderung im Intervall* in manchen Fallen pathogenetisch wesentlich wirksamer als die Behinderung im eigentlichen Anfall die Folgen fur das Parenchym sind schwerer als die der relativ kurz dauernden Lungenblahung

Trotzdem hier nur die Verengerung der Luftwege und nicht die Genese des Asthmas im Vordergrund der Betrachtung steht sei doch ein Hinweis erlaubt auf die Bedeutung des myoelastischen Systems (Sturm) in der Genese von Asthma *und* Emphysem d h eine zentrogene diencephale Auslosung mit direktem Angriffspunkt am respiratorischen Parenchym selbst

Neuerdings hat Amell Sans wieder die Aufmerksamkeit auf die Struktur der intraalveolaren Septen gelenkt Er hat darin ein uberaus reich angelegtes System von Reticulin nachweisen konnen, ein System das er als codynamisch zur Wirkung der glatten Muskelfasern betrachtet und dem also ein gewisser Grad von Kontraktilitat zukommt Der Autor sieht in der Basal Membran der membrane vitreuse von *Letulle* ebenfalls ein *kontraktiles Gebilde*, analog der Membran des renalen Glomerulums

Wenn also das Terminalsystem der Alveolen zwar keine Muskelfasern im Sinne von Baltisberger enthalt so ware es trotzdem zu Kontraktionen befahigt Es wird angenommen dass dieses System den Tonus der Lungen reguliert Dieser steht unter den verschiedensten nervosen Einflussen Expirations reflex von Hering Breuer etc und ebenso mit grosster Wahrscheinlichkeit unter demjenigen von Antigenen die somit auch an dieser Stelle des Systems d h an der Alveolarwand selbst zur Auswirkung kommen konnten

Das Emphysem ist damit wohl eines der schlagensten Beispiele wie rein funktionell allergische und in der Folgezeit sehr haufig psychogene Momente sich somatisch auswirken konnen Das so erzeugte Emphysem unterscheidet sich weder anatomisch noch funktionell grundsatzlich von andern Emphysemformen die durch Stenose der feinen abführenden Luftwege zustande kommen

Sind die somatischen Veranderungen einmal so weit gediehen dass es zum Dauer Emphysem gekommen ist so wird auch die ganze Kette der pathologischen Veranderungen ausgelost die diese Schadigung charakterisiert so die ungleiche Beloftung der verschiedenen Lungenabschnitte der ungenugende Kontakt der Atemluft in den durch Septen Schwund erweiterten Alveolen mit der Rarefikation der Kapillaren Die Verengerung des Strombettes im kleinen Kreislauf die zum Cor pulmonale fuhrt das als Kompensationserscheinung aufzufassen ist und fur lange Zeit auch als solche wirkt bis es endlich zur Dekompensation des Cor pulmonale

Durch die neue Bezeichnung Cor pulmonale im Zusammenhang mit den Lungenfunktionsprufungen hat das Studium der Herzbeteiligung bei Lungenaffektionen besonders beim Emphysem neue Auftriebe erhalten Diese Zustande sind aber klinisch und pathologisch anatomisch schon sehr lange bekannt

Vor mehr als 100 Jahren (1850) hat Ditrich beim Studium der Sklerose der Arteria pulmonalis zwei Formen unterschieden eine Pulmonalissklerose bei Mitrallasion bei der damals sogn Lungenhypertrophie = Blutüb rfüllung (Skoda) und eine solche bei *Atrophie der Lunge als offenkundig bei Emphysem*

Ist dieses Stadium erreicht so treten die pathogenetischen Momente in den Hintergrund Der Patient ist ein Herzkranker geworden bedroht von Rechts Insuffizienz deren weitere Entwicklung gegeben ist

Therapie Die einmal eingetretene alveolare Schadigung kann direkt kaum wesentlich beeinflusst werden Das Hauptgewicht liegt neben der Behandlung der Komplikationen auf der Prophylaxe Verhinderung oder Verminderung der Ventilationsdrosselung (mechanische spastische allergische entzundliche) Desensibilisierung spezifische oder auch unspezifische Reizkorpertherapie wozu auch der Klimafaktor gehort Bezuglich Therapie des Asthmas sei nur nochmals auf eine vernunftige Psychotherapie verwiesen wozu auch eine richtige Atemtechnik gehort die zur Zeit in den Handen eines besonders geschulten Personals liegt

Jodkali bleibt ein ausgezeichnetes Medikament bei Affektionen des Bronchialbaumes Parasympathisch angreifende Medikamente wie Atropin etc vorausgesetzt dass die austrocknende Wirkung auf die Bronchialschleimhaut nicht zu stark in Erscheinung tritt

Infektallergische Zustande oder Infekte also itis werden in der ublichen Weise behandelt doch sollen die Sulfonamide nicht vergessen werden

Die Antibiotica Anwendung erfolge systematisch mit Penicillin beginnend wenn die Resistenzbestimmung es gestattet eingedenk der Moniliasen und der Tatsache dass Antibiotica über die Grenzen der Behandelten hinaus Ruckwirkungen auf die ganze Umgebung haben konnen Mund und Rachenschleimhaut des Wartepersonals etc werden mit resistenten Erregern beschickt vor allem Staphylokokken die besonders im Milieu des Krankenhauses gefahrlich werden konnen

Vielversprechend scheint die hormonale Therapie zu sein Wahrend ACTH beim schweren Asthmaanfall wenn alles versagt fast schlagartig wirkt konnen ACTH und Cortison aber bei Herzinsuffizienz wegen der Wasserretention keine Anwendung finden Dagegen erzielt *Meticorten* etc bei Lungeninsuffizienz manchmal erstaunliche Besserungen

ZUSAMMENFASSUNG

Das chronische Lugenemphysem Symptomenkomplex viel mehr als Krankheitseinheit hat *eine* seiner pathogenetischen Wurzeln in der chronischen Stenose der feinern Bronchialaeste Die Stenosen konnen sowohl entzundlich bedingt sein wie allergisch wie funktionell neuro bzw psychogen

Massgebend fur die Emphysem Entstehung sind Ausbreitung und Dauer der Stenosen

Ob nicht auch andere Angriffspunkte der Noxen (Antigene und andere) speziell solche die in der Alveolarwand selbst angreifen in Frage kommen steht zur Zeit noch zur Diskussion wobei das myoelastische System (Baltisberger Sturm) und ein in die Alveolarwand lokalisiertes kontraktiles Element Reticuline genannt (Amell Sans) in Betracht kommen

Allergische Zustande wie Asthma und sog eosinophile Bronchitis nehmen in der Emphysem Genese eine hervorragende Stellung ein Beim Asthma ist nicht nur der klassische Anfall sondern auch das *Intervall* in der Emphysem Genese zu berucksichtigen Das Emphysem dieser Genese ist eines der klassischen Beispiele somatischer Schaden bedingt durch

psychische Einwirkungen (psychisch fixierte Reaktion im Sinne bedingter Reflexe)

Es handelt sich beim Emphysem um irreversibel gewordene haufig progrediente schwere Veranderungen die zu Erschwerung des Gasaustausches zu erhohtem Druck in der Arterie pulmonalis zu Cor pulmonale und schliesslich zu dessen Dekompensation fuhren Die Therapie hat sich vor allem gegen die Entstehung der Stenosen zu richten Sie ist eine anti infektiose antallergische anti spastische psychotherapeutische und hormonale

RÉSUMÉ

L emphyseme chronique beaucoup plus un syndrome qu une entite morbide, a comme cause pathogénique essentielle la sténose chronique des bronchioles Cette stenose peut etre conditionnée soit par une inflammation chronique soit par une cause allergique soit enfin par une alteration fonctionnelle neurovégetative ou psychique

Ce qui est essentiel dans la production de l emphyseme c est l extension et la duree des processus stenosants Abstraction faite des élements agressifs (antigenes ou autres) susceptibles d agir sur d autres éléments anatomiques et plus specialement sur la paroi alvéolaire elle meme la discussion se limite actuellement au role possible d une part du systeme myo élastique (Baltisberger Sturm) et d autre part de la substance contractile localisée dans la paroi alveolaire appelée réticuline (Arnell Sans)

Les états allergiques tels que l asthme et la bronchite a éosinophiles jouent un role prédominant dans la genese de l emphyseme Dans l asthme ce n est pas tellement la crise elle meme mais l intervalle entre les crises qui doit etre considere comme facteur génerateur d emphyseme L emphyseme qui relève de cette origine est un exemple classique de lesions somatiques provoquées par des influences psychiques du type des reflexes conditionnels fixes

Il s agit dans l emphyseme d altérations devenues irreversibles et progressives qui conduisent a des troubles des echanges gazeux a une augmentation de la pression dans l artere pulmonaire au cœur pulmonaire chronique et enfin à la décompensation cardiaque

La thérapie doit etre orientee avant tout contre l organisation du processus *stenosant Elle doit etre anti infectieuse anti allergique anti* spasmodique psychique et hormonale

SUMMARY

Chronic emphysema is rather a syndrome than a disease which is caused mainly by chronic stenosis of the bronchioles This stenosis can be caused either by chronic inflammation or by allergy or finally by a change in autonomic nervous or psychic function

The chief factor in the production of emphysema is the extent and duration of the stenosing process Without considering aggressor factors (antigens etc) acting mainly on the alveolar wall the discussion will be

limited to the musculo elastic system (Baltisberger Sturm) and to the contractile substance called reticulin localised in the alveolar wall (Amell Sans)

Allergic states such as asthma and eosinophilic bronchitis play an important role in the development of emphysema In asthma it is not so much the crisis itself but the intervals between crisis which must be considered as the dominant factor producing emphysema Emphysema of this origin is a classical instance of organic lesions produced by psychic influences caused by conditioned reflexes

The lesions of emphysema are progressive and irreversible leading to difficulties of gaseous exchange to hypertension in the pulmonary artery chronic pulmonary heart and finally to heart failure

Therapeutics must be concerned primarily with preventing the stenosis processes It should be anti infective anti allergic antispasmodic psychic and hormonal

RESUMEN

El *enfisema crónico* en realidad un síndrome más que una enfermedad tiene como causa patogenica esencial la estenosis crónica de los bronquiolos Esta estenosis puede ser producida ya sea por una inflamación crónica por una causa alérgica o por una alteración funcional neurovegetativa o psiquica

Lo esencial en la producción de un enfisema es la extensión y la duracion del proceso Haciendo abstraccion de los elementos agresivos (antígenos y otros) que pueden actuar sobre los elementos anatómicos y especialmente sobre las paredes alveolares la discusión se limita actualmente al posible papel desempeñado de una parte por el sistema mio elástico (Baltisberger Sturm) y de otra parte por la sustancia contráctil localizada en la pared alveolar llamada reticulina (Arnell Sans)

Los estados alergicos tales como el asma y la bronquitis acompanada de eosinofilia tienen una importancia predominante en la génesis de enfisema En el asma no es tanto la crisis misma sino los intervalos entre las crisis los que deben ser considerados como los factores generadores El enfisema que tiene este origen es un ejemplo clasico de las lesiones somaticas provocadas por influencias psíquicas del tipo de los reflejos condicionados

Se trata en el enfisema de alteraciones irreversibles y progresivas que conducen a trastornos de los intercambios gaseosos a un aumento de la presión en la arteria pulmonar al cor pulmonar crónico y a la falta de compensacion cardiaca

La terapéutica debe estar dirigida sobre todo a evitar la instalación del proceso estenosante Debe ser anti infecciosa antialérgica antiespasmódica psiquica y hormonal

DEATH FROM BRONCHIAL ASTHMA

by

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(From the Department of Internal Medicine Washington University Medical School and the Barnes Hospital St Louis Missouri)

Before the year 1930 death caused primarily from bronchial asthma was considered a rare event This belief had been recorded repeatedly for almost one hundred years Trousseau Andral and Oliver Wendell Holmes affirmed it and it was stated in the text books of the day It was not until 1922 however that a systematic investigation was made Huber and Koessler (1) then published a review of the literature of autopsied cases of asthma and could find but fifteen and added several more A later analysis of these reports indicated that many of them did not represent death primarily from asthma so that by the year 1930 only 22 proven cases were on record

Even if one applies several probabilities that would enhance the small number of reported fatalies it would seem difficult to assume a position other than acceptance of the fact that death primarily from bronchial asthma was an infrequent event at that time

Certainly this has not been the case in recent years and particularly so during the last decade As with unusual disorders when single reports eventually are recorded in series of scores of cases publications of the subject thereafter occur only occasionally This has been true of death from asthma which no longer seems to attract attention

The discrepancy between the older and the newer experiences initiated this study Whether this difference is true or only apparent is almost impos ible to prove because the data particularly of the few earlier cases are not sufficient to meet all the requirements of biostatistics However with the impression that a difference does exist inquiry was made into the circumstances that surround it

The term death from bronchial asthma refers to patients who expired during a paroxysm or were found dead shortly thereafter as interest was centered on the natural history of the disease In all cases post mortem examinations indicated that death was due primarily to asthma and not to one of its complications Discarded also were those in whom the administration of sera or drugs were apparently responsible for exitus

The material for this report was assembled from two sources those appearing in the literature and those from a study of a given hospital population from which detailed clinical records as well as those of autopsies extending over a period of over thirty years were examined They embrace the early period of but few deaths as well as current experience In all there are 174 reports

PATHOGENESIS

For many years as is well known the direct mechanism that produces an asthmatic paroxysm was debated However as sufficient post mortem material became available it was determined that occlusion of the bronchi is due principally to mucus secreted from glands in the bronchial walls Constriction of the intrinsic bronchial musculature is probably a contributory factor This is indicated by experimental studies as well as the typical finding of muscle hypertrophy brought about presumably by excessive action a work hypertrophy In all probability bronchospasm contributes considerably to asthmatic death in infants who have a peculiar metaplasia of the bronchial epithelium which is heaped up and apparently causes some narrowing of the airway A superimposed severe bronchospasm may well cause asphyxia although in at least two instances excessive mucus in the bronchioles have been described

It is a singular circumstance that although the cause of death in asthma has for some years been recognized as due to excessive mucus there has been almost no published systematic study of this material or of the glands that secrete it Werner (2) found that normal bronchial mucus contains principally nitrogen several carbohydrates and sialic acid but there is good reason to suspect that the abundant tough mucilaginous sputum of asthma may have a different structure In various post mortem reports the mucous glands have been described as normal as well as scant in numbers hypertrophied degenerated or normal in appearance No account of observation of differential staining or other detailed characteristics are as yet avai [illegible]

for mucus accummulation

The mechanism which terminates life in bronchial asthma is not entirely clear Two principal modes of exitus are recognized One is evident asphyxia wherein breathing becomes increasingly labored cyanosis intensifies and drowsiness to the point of unconsciousness occurs evidently from respiratory acidosis gasping respirations appear and the heart continues to pulsate after the last breath The situation differs little from death primarily from emphysema

The second manifestation is peripheral vascular collapse This occurs during a paroxysm and usually comes on quite suddenly The mechanism remains unexplained There is no evidence that it is due to right sided heart failure or sudden change in pulmonary function Although it has been ascribed to sudden occlusion of a main bronchus by mucus there is

little support for this theory from post mortem examinations It has been suggested that the situation may be related to pressure changes in the pul monary artery that affect reflexes in that structure A systematic study of this phenomenon is needed

Comment may be made on the effect of sedation in severe asthma Although emphatic statements have been recorded regarding the dangers involved it is difficult to secure a clear evaluation of the problem Certainly oversedation will depress the respiratory center and morphine has a mild cholinergic action which may induce some degree of bronchospasm In a few recorded instances large amounts of sedatives undoubtedly hastened exitus The statement however that sedatives once well tolerated may develop an enhanced pharmacological effect is a theory difficult to establish if controls are considered The same holds true for the declaration that morphine is the principal cause of death in asthma In the material that was studied some patients tolerated substantial quantities of opium deri vatives without apparent ill effect Particular attention was paid to this problem by one observer who could find no obvious danger in the use of morphine in conventional therapeutic doses Some decades ago morphine was a drug of choice for asthma and addiction in which large doses were well tolerated was not uncommon The question needs a clearer evaluation The implied dangers of large doses of epinephrine of steroids and of oxygen also have been pointed out

ANALYSIS OF DATA

Age at death

Of the 174 cases of death primarily from asthma 13 died in infancy before the age of two and three others before they were five years of age During the following 30 years of life there were 23 fatalities in all but 39 before the age of 35 Between 35 and 65 inclusive 125 deaths occured 70 percent of the total Ten patients died after age 65 (Fig 1) In 1953 Earle (4) reviewed the literature on death from asthma and the findings recorded here in a larger series correspond to his

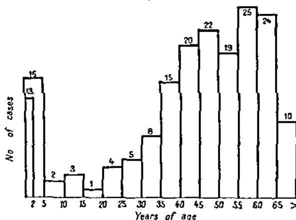


Fig 1

Duration of asthma

Well over one hundred years ago Andral quoted a maxim which he said was then old asthma is a brevet of long life This seems in keeping with the paucity of recorded deaths In the series here reported quite the reverse is true Of the 151 cases in which the duration of symptoms was stated 39 excluding infants died within one year of onset 59 within two years and 84 or 55 percent of the total within five years (Fig 2) There are few chronic diseases that compare in malignancy with bronchial asthma since death often occurs within one year of its onset The finding that most fatalities appear within five years and that these occur largely after the age of 40 years point up the potential seriousness of asthma in individuals of middle age For each death there must be hundreds of severely ill patients who survive

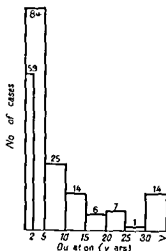


Fig 2

DISCUSSION

From these observations two facts seem apparent namely, death from asthma is not uncommon and individuals of middle age and older are the ones that usually succomb From case reports the few deaths that were [illegible]

That this is not the case is indicated by an examination of the records of the Barnes Hospital which admits only adults The average age of patients with asthma on admission in the year 1924 was 35 years whereas in 1954 it was 50 years The difference in control cases over that period was but four years

TABLE I

Increase in the average age of asthmatics admitted to the Barnes Hospital

YEARS	AVERAGE ADMISSION AGE	CONTROLS (unselected cases)
1924	35	46
1924 1933	39	
1934 1943	45	
1944 1953	49	
1954	50	50

This gradual increase in the ages of asthmatics admitted to the hospital as well as the ages of onset of symptoms are set forth in more detail in Table 2

TABLE II

First 20 Consecutive Cases of Bronchial Asthma Admitted to the Barnes Hospital in the Years 1924 and 1954

YEAR 1924			YEAR 1954		
sex	age	age of onset	sex	age	age of onset
F	48	42	F	64	63
F	25	24	M	38	37
F	26	21	M	54	53
F	46	44	F	37	31
F	17	15	F	32	23
F	37	32	F	44	3
F	65	50	M	59	58
M	32	30	M	63	62
F	28	26	F	47	46
M	25	22	F	55	41
F	20	16	M	54	52
F	38	14	F	24	21
F	34	15	F	78	75
F	29	21	M	51	49
F	21	17	F	59	9
M	38	14	F	54	24
F	50	43	M	24	22
F	37	29	F	51	50
M	59	34	M	50	45
F	24	21	F	59	44
Averages	35	26.5		50	40.5

In 1924 an early date in the history of Allergy according to the records of the hospital many younger patients were admitted for diagnostic study although an out patient clinic was already in existence The number of seriously ill asthmatics was not large and no death from the disease occurred

before the year 1926 eleven years after the hospital had been in operation Then apparently as out patient attention became more effective more hospital beds gradually became occupied with asthmatics who entered primarily for treatment and these constituted a sicker group

There were 1484 patients admitted with a primary diagnosis of bronchial asthma over a period of 31 consecutive years Three types of asthma were recognized One was the typical atopic variety with its onset usually in the earlier years of life and in which a specific allergen was commonly identified The second was the older patient who had carried his atopic asthma for many years and in whom symptoms may or may not have diminished in severity and the usual pulmonary complications were frequent The third type was in the patient whose asthma began in middle age or later In a small but undetermined number of these patients a specific allergen was the cause of symptoms In the remainder asthma conformed to the so called non atopic or infectious or intrinsic type

This form of asthma was identified by its later age of onset its very frequent association with infection of the respiratory tract the absence of identification of a specific allergen and the episodes of poorly controlled paroxysms which brought the patient to the hospital On the other hand the comparatively high incidence of a family history of asthma the frequent association of vasomotor rhinitis and the typical symptoms link this type closely to atopic asthma

It is difficult to escape the conclusion that of so called nonstopic asthma has come into more prominence in recent years Two circumstances support this impression One is the fact that there is little mention of its existence prior to the year 1940 That it did exist is obvious from hospital records as well as from reports of fatal cases but such cases were not apparently numerous In three text books on asthma appearing early in the last decade very little attention was paid to this important type of asthma and some publications of that day questioned or even denied its existence

Secondly from the Barnes Hospital records the incidence of patients who develop asthma after the age of 40 has steadily mounted during the years This is indicated in Table 3

TABLE III

Percentage of Asthmatics who Developed Symptoms after 40 Years of Age

YEA S	PERCENT
1924	20
1924 1933	27
1934 1943	40
1944 1953	47
1954	56

It should be stated that the ratio of patients with asthma to that of the general medical admissions had not increased over the period represented in Table 3 There is no indication that the increased number of admissions

of patients whose asthma began in middle age is identified particularly with atopy Consequently one may conclude that there has been a shift in emphasis over the years in the direction of more hospitalized patients with non atopic asthma at the expense of other types The increase in the incidence of such cases which contribute largely to the fatalities may readily explain the apparent rise in the death rate

No similar phenomenon in the long recorded history of asthma was found Why in the matter of a few decades the disease in spite of improved treatment should have become a much more serious disorder remains unexplained One interesting coincidence which conceivably may have relevance concerns experience with periarteritis nodosa which has been identified with allergy both in terms of asthma and hypersensitivity to sulfonamide and other drugs

The apparent recognition of the marked increase of reported instances of periarteritis after the year 1938 which corresponds to the period during which non atopic asthma also was increasingly identified is a striking parallelism although it is not possible to make an accurate comparison because the dates of onset for each disorder are often missing Whether there may be a close association between the two in terms of underlying mechanisms such as the participation of autoantibodies that is suspected in periarteritis remains as yet a purely speculative thought

SUMMARY

This report is based on 174 patients in whom death was caused primarily from bronchial asthma All cases succumbed during a paroxysm or were found dead shortly thereafter Excluded were patients known to be sensitive to an allergen that had been administered shortly before death those that had received undue sedation and those in which any complication contributed essentially to death In all instances autopsy findings confirmed the diagnosis Material was derived from a survey of the records of over 1500 adult patients that had entered the Barnes Hospital primarily for asthma over a consecutive period of 3_ years as well a reports from the literature

The following data are submitted

1 Although not subject to statistical analysis there is good reason to believe that the death rate from asthma has increased since the year 19_5

2 There has been a progressive rise in the average age of hospitalized adult asthmatics (from age 35 in 19_4 to age 50 in 1954) as well as in the average age of onset of asthma (age 25 in 1924 to age 39 in 1954)

3 Seventy eight per cent of those that died were over 35 years of age

4 The reason for this apparent rise in death rate is not known but there is a close parallel over the period studied between the curves of incidence of fatal asthma and that of periarteritis nodosa with which it is associated

5 That bronchial asthma may become malignant is indicated by the fact that its duration was less than two years in 37 per cent of the fatal cases and in 57 per cent the duration was less than five years

Mechanisms of death are discus ed

RÉSUMÉ

Ce rapport est basé sur l etude des 174 malades dont la mort a eu pour cause principale l asthme bronchique Tous ces malades moururent pendant la crise asthmatique ou peu de temps apres

Il n a pas été tenu compte des malades sensibilisés a une substance allergenique connue et ayant reçu cette substance peu auparavant ni de ceux ayant absorbé des doses excessives de sedatifs ni de ceux pour lesquels d autres complications pathologiques ont pu etre une cause essentielle de mort Dans tous ces cas les résultats des autopsies sont venus confirmer le diagnostic

Nous avons puisé notre documentation dans les archives médicales de l Hopital Barnes et dans la litterature medicale Nous avons étudie les cas de 1500 malades hospitalisés leur principale maladie étant l asthme bronchique cette étude porte sur une periode de trente deux ans

Nous vous soumettons les données suivantes

1° Bien qu il n y ait pas de statistiques à l appui il existe de bonnes raisons de croire a l augmentation du taux de mortalité par asthme bronchique depuis 1925

2° On constate une augmentation progressive de l âge moyen des asthmatiques hospitalisés 35 ans en 1924 contre 50 ans en 1954 L âge des malades subissant leur premiere atteinte d asthme a lui aussi augmenté 25 ans en 1924 et 39 ans en 1954

3° Pour les cas *mortels* 78 % *des malades étaient âgés de plus de trente* cinq ans

4° Les raisons de cette apparente augmentation du taux de mortalite ne sont pas connues cependant on remarque que pendant cette meme periode la courbe des déces dus à la périartérite noueuse affection qui accompagne souvent l asthme est très semblable à celle de l asthme lui meme

5° L asthme bronchique peut revetir un caractere de malignité comme l indiquent les chiffres suivants la duree de la maladie a eté de moins de deux ans dans 37 % des cas mortels de moins de cinq ans dans 57 % de ces cas

Les mecanismes de la mort par l asthme seront aussi etudies

ZUSAMMENFASSUNG

Diese Veroffentlichung beruht auf dem Studium von 174 Krankheitsfallen in denen der Tod hauptsächlich an Asthma bronchiale erfolgte Alle diese Kranken starben wahrend der asthmatischen Krisis oder kurz danach

Diejenigen Krankheitsfalle wurden nicht berucksichtigt bei denen eine Sensibilisierung gegen eine verabreichte Allergensubstanz bekannt war auch diese die exzessive Dosen von Sedativa bekommen hatten oder bei denen andere pathologische Komplikationen eine wesentliche Todesursache sein konnten In allen Fallen bestatigte das Resultat der Autopsie die Diagnose

Unsere Belege entnahmen wir den medizinischen Archiven des Barnes Hospitals und der medizinischen Literatur Wir untersuchten 1500 Fälle von ins Krankenhaus eingelieferten Patienten bei denen als hauptsächliche Erkrankung Asthma bronchiale bestand Diese Studie erstreckt sich über eine Zeitperiode von 32 Jahren

Die Ergebnisse sind wie folgt

1 Obwohl es keine Statistik zu unserer Unterstützung gibt bestehen doch gute Gründe anzunehmen dass die Mortalität des Asthma bronchiale seit 1925 zunahm

2 Man kann eine progressive Zunahme des mittleren Alters der ins Hospital eingelieferten Asthmatiker feststellen Im Jahre 1924 waren es 32 Jahre im 1954 hingegen 50 Jahre Das Alter der Patienten mit dem ersten Asthmaanfall nahm ebenso zu 1924 war es bei 25 Jahren 1954 bei 39 Jahren

3 *Bezüglich der Todesfälle waren 78 % der Kranken älter als 35 Jahre*

4 Die Gründe für diese Mortalitätzunahme sind nicht bekannt indessen kann man feststellen dass während derselben Zeitperiode die Todeskurve der Periarteriitis nodosa — eine Erkrankung die oftmals Asthma begleitet — sehr änlich der Asthmakurve ist

5 Asthma bronchiale kann bösartige Verlaufssformen annehmen wie folgende Zahlen es zeigen die Krankheitsdauer der tödlich endenden Fälle betrug in 37 % weniger als 2 Jahre in 57 % weniger als 5 Jahre Der Mechanismus des Asthmatodes wird ebenfalls untersucht

RESUMEN

Esta comunicación está basada sobre observaciones efectuadas en 174 pacientes en los cuales la muerte fue debida fundamentalmente al asma bronquial En todos los casos la muerte se produjo durante una crisis o poco tiempo despues de ella Han sido excluidos aquellos pacientes en los que la muerte tuvo lugar poco tiempo despues de la administración de un alergeno al cual eran sensibles como asimismo aquellos que recibieron sedantes en dosis excesivas o en los que cualquier complicación contribuyo sustancialmente al desenlace En todos los caso el diagnostico ha sido confirmado por la autopsia Los casos estudiados han sido seleccionados entre las historias clínicas de mas de 1 500 pacientes asmaticos adultos atendidos en el Hospital Barnes durante los ultimos 32 anos y también se han incluido los casos citados en la literatura

Se presentan las siguientes conclusiones

1 Aunque se carece de estadísticas suficientes hay buenas razones para suponer que la mortalidad por asma ha aumentado desde el ano 19-5 hasta la fecha

2 Ha habido un progresivo aumento en la edad media de los adultos asmaticos hospitalizados (de 35 años en 1924 a 50 años en 1954) como asi tambien en la edad media de aparición del asma (25 años en 19-5 a 39 años en 1954)

3 En el 78 % de los casos de muerte los pacientes tenian mas de 35 años

4 Se ignoran las razones del aparente aumento de mortalidad pero se hace notar que existe un estrecho paralelismo durante el periodo estudiado

entre las curvas de incidencia de asma fatal y de periarteritis nodosa con la cual está asociado.

5. La posibilidad de que el asma bronquial pueda tener una evolucion maligna se traduce en el hecho de que su duracion es inferior a 2 años en el 37 % de los casos fatales e inferior a 5 años en el 57 % de los casos. Se discuten los mecanismos causales de la muerte.

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DEATH FROM BRONCHIAL ASTHMA DISCUSSION

by

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We have the impression that some clinicians consider the diagnosis of status asthmaticus a straightforward one but this is not always so There is sometimes considerable clinical difficulty in distinguishing the asthmatic from the bronchitic and it is obvious that even true asthmatics dying in acute respiratory or cardiac failure are not of necessity dying from status asthmaticus The presence of cardiac failure to us rules out a diagnosis of uncomplicated status asthmaticus for we have never seen cardiac failure in a patient in whom later the post mortem examination showed that death was from uncomplicated status asthmaticus In the literature post mortem findings of deaths recorded as from asthma have included not only those with the characteristic finding of widespread plugging of the bronchi with a non purulent mucus but also cases in which deaths were from suppurative bronchitis and even broncho pneumonia It is indeed sometimes quite difficult to distinguish status asthmaticus from acute suppurative bronchitis but these are two separate pathological conditions and clinicians need to differentiate them especially since the advent of cortisone and corticotrophin

There is still a need to correlate closely clinical and pathological findings in asthmatics dying from acute respiratory failure and a need to clearly define our nomenclature

We would define asthma as recurrent spontaneous attacks of dyspnoea and wheeziness commonly occurring at night and due to a characteristic

important and characteristic features are the plugging of the bronchi with a thick tenacious mucus (Editorial J Allergy 1952) and the eosinophiles found in the mucus and in the walls of the bronchi (Cooke 1947 Walton et al 1951 Walzer and Frost 1952 Cardell 1956)

entre las curvas de incidencia de asma fatal y de periarteritis nodosa con la cual está asociado

5 La posibilidad de que el asma bronquial pueda tener una evolucion maligna se traduce en el hecho de que su duracion es inferior a 2 años en el 37 % de los casos fatales e inferior a 5 años en el 57 % de los casos

Se discuten los mecanismos causales de la muerte

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3 HILDING (A C) *The relations of ciliary insufficiency to death from asthma and other respiratory diseases* Ann Otol Rhin and Laryngol 52 5 1943

4 EARLE (B V) *Fatal bronchial asthma a series of fifteen cases with a review of the literature* Thorax 8 195 1953

from official figures one of us (D A W) has attempted to trace all deaths from status asthmaticus occurring in Cardiff and district a population of some 300 000 In 1951 13 undoubted asthma deaths occurred in 1952 12 in 1953 14 in 1954 12 in 1955 14 and in 1956 5 deaths From 1951 to 1955 inclusive there was an average of 13 deaths per year i e a death rate of 5 per 100 000 as against an official rate of 6 per 100 000 (1956 is excluded as an exceptional year possibly due to the use of ACTH and cortisone) It is suggested that these findings in a population of 300 000 the size of which obviously precludes one person from seeing every death from asthma supports the general validity of the Registrar General s Reports The details are set out in Table II

TABLE II

Deaths from asthma per 100 000 population

	1951	1952	1953	1954	1955	1956
Registrar General s Inset figures						
Males	8 68	6 59	6 44	5 85	5 79	5 23
Females	7 53	5 41	5 93	5 36	5 08	5 48
Total	8 08	5 98	6 17	5 60	5 38	5 36
Clinical Findings at Cardiff						
Males	4 33 (5)	1 72 (2)	5 07 (6)	3 37 (4)	2 52 (3)	(3)
Females	6 25 (8)	7 78 (10)	6 24 (8)	6 19 (8)	6 95 (9)	(2)
Total	5 34 (13)	4 90 (12)	5 68 (14)	4 84 (12)	4 83 (12)	

(The figures in bracket are the numbers of cases of deaths from br nchi l thma)

PATHOLOGY

We have been fortunate in Cardiff in our association with Professor Gough who introduced a new technique (Gough and Wentworth 1949) which enables a relatively thin section of a whole lung to be mounted on paper and from such large lung sections the absence or presence and extent of destructive emphysema can be seen The striking and at first surprising finding in deaths from status asthmaticus when lungs were examined by this technique was the absence of destructive emphysema (Gough 1952) Of a consecutive series of 17 cases of fatal status asthmaticus bullous emphysema was present in only 1 and in this case there was an associated severe bronchiectasis In the other cases the lungs were simply over distended just like those of a person drowned (Gough 1955) One of us (J G L) (until recently a member of Professor Gough s department) has now examined in detail the autopsy material of 25 adults all of whom had been diagnosed clinically as having died from status asthmaticus and all of whom

fulfilled the accepted pathological requirements The series consisted of 19 females and 6 males giving a female preponderance of 3 to 1 Although initially in some of the cases the asthma was clinically considered to have been extrinsic or allergic all were considered to have become infective or intrinsic in type before their deaths A characteristic feature in the history was of a cold going to the chest and bringing on severe asthma although objective evidence to support this infective history was absent in most cases This applied not only to fatal attacks but to many of their preceeding ones The duration of asthma averaged 21 years and in two cases was over 40 years The average age at death was 56 years 9 cases were over 60 years All were obviously cases of severe asthma all had had repeated attacks of status asthmaticus prior to their final attack The average length of stay in hospital was 13 1/2 weeks

The lungs in all these 25 cases of status asthmaticus were hyperexpanded but in none of the 19 females was there any destructive emphysema nor in 4 out of the 6 males The 2 males with areas of destructive emphysema (aged 53 and 71 years) had both been diagnosed as having bronchitis as well as asthma and in both an area of localized bronchiectasis was found In our series we (J G L) find as have others (Walzer and Frost 1952) that the cellular reaction in the bronhci and bronchioles takes the form of an infiltration with eosinophile cells lymphocytes and plasma cells neutrophiles are always less than 10 % of all polymorph cells and often they are absent Thus the cellular reaction has more allergic than infective characteristics Heavy eosinophilic infiltration appears to be the hallmark of severe active asthma We observe (as did Cardell 1956) that when death occurs a week or so after the last attack from causes other than asthma the eosinophilia of the bronchi is either absent or so slight that the pathological changes are indistinguishable from those of chronic bronchitis with no history of asthma

We (J C L) have examined partly by serial sections the distribution of thea llergic reactive changes in this series of 25 status deaths and find as have others that the reaction is maximal in the medium and small bronchi An additional observation we have made is that the intensity of the reaction diminishes in the bronchioles and cell infiltration can not be found affecting respiratory bronchioles (except in one of the cases with emphysema) Thus the pulmonary parenchyma is unaffected

The findings in cases of clinical bronchitis with destructive centrilobular emphysema (Leopold and Gough 1957) are completely different The inflammatory changes are infective in pattern occur at parenchymal levels cause permanent damage to respiratory bronchioles which develop a destructive emphysema The work at Cardiff therefore suggests that destructive emphysema is not likely to occur in asthma which is uncomplicated by episodes of infective bronchiolitis We would however emphasize that the pathological identification of tissue destructive emphysema is not as easy as would first seem

Heppleston (1953) of Professor Gough s department has confirmed by serial section studies the suggestion of Hartroft (1945) that routine histological sections of the lung can easily be misinterpreted as showing destruction of alveolar walls when none exists and special techniques may be necessary for correct assessment

In conclusion we would suggest that death from asthma not altogether rare in infants is not uncommon over the age of 30 years We have found he clinical and pathological findings reasonably predictable in our female asthmatics a number dying in asthma and without destructive emphysema but in males the clinical course and pathological findings have been less predictable relatively fewer dying in status asthmaticus and in some destructive emphysema has been present as a complication Quite a high proportion of our male asthmatic patients do go on to bronchitis (with bronchiolitis) and destructive emphysema often losing their asthma when this happens and dying of bronchitis and emphysema with terminal pneumonia suppurative bronchitis or cardiac failure But these of course are not deaths in asthma but deaths in asthmatics who have developed chronic bronchitis and emphysema Perhaps the problem of bronchiolitis complicating asthma is a special problem in England where our prevalence and death rates from bronchitis are so high (Oswald 1958)

It is with pleasure we acknowledge our indebtedness to Professor J Gough and Dr A G Heppleston Pathology Department Welsh National School of Medicine Cardiff

SUMMARY

The official death rate from asthma in England and Wales during the 8 years 1949 to 1956 was 6 per 100 000 and evidence supporting the general validity of this figure is given An analysis of 101 deaths from status asthmaticus at Cardiff shows the risk of death asthma not altogether rare in infants notably increases after the age of 30 years Over two thirds were females Of the adults 82 % had had asthma for over 5 years 61 % over 10 years and 47 % over 20 years The asthmatic subject to status asthmaticus is especially at risk.

Results of a study by large lung sections (Gough & Wentworth technique) and by serial sections of the bronchi and bronchioles of autopsy material of 25 adults 19 females and 6 males all of whom died in undoubted status asthmaticus are presented The hallmark of death from active asthma is widespread plugging of the bronchi with a thick gelatinous mucous containing eosinophile cells with heavy eosinophilic infiltration of the walls of the bronchi These changes are maximal in the medium and small bronchi A striking and apparently previously unobserved finding is that the cellular reaction of the bronchi and bronchioles did not extend to the terminal bronchioles in uncomplicated asthma All these lungs were hyperexpanded but in none of the females nor in 4 of the 6 males was there any destructive emphysema Evidence is presented supporting the viewpoint that destructive emphysema is not likely to occur in asthma which is uncomplicated by episodes of infective bronchiolitis

RESUME

Pendant une periode de huit ans de 1949 a 1956 le taux de mortalite pour l asthme a ete de 6 par 100 000 habitants et des preuves sont apportees pour corroborer ces chiffres Une étude de 101 cas d asthmes mortels

fulfilled the accepted pathological requirements The series consisted of 19 females and 6 males giving a female preponderance of 3 to 1 Although initially in some of the cases the asthma was clinically considered to have been extrinsic or allergic all were considered to have become infective or intrinsic in type before their deaths A characteristic feature in the history was of a cold going to the chest and bringing on severe asthma although objective evidence to support this infective history was absent in most cases This applied not only to fatal attacks but to many of their preceeding ones The duration of asthma averaged 21 years and in two cases was over 40 years The average age at death was 56 years 9 cases were over 60 years All were obviously cases of severe asthma all had had repeated attacks of status asthmaticus prior to their final attack The average length of stay in hospital was 13 ½ weeks

The lungs in all these 25 cases of status asthmaticus were hyperexpanded but in none of the 19 females was there any destructive emphysema nor in 4 out of the 6 males The 2 males with areas of destructive emphysema (aged 53 and 71 years) had both been diagnosed as having bronchitis as well as asthma and in both an area of localized bronchiectasis was found In our series we (J G L) find as have others (Walzer and Frost 1952) that the cellular reaction in the bronhci and bronchioles takes the form of an infiltration with eosinophile cells lymphocytes and plasma cells neutrophiles are always less than 10 % of all polymorph cells and often they are absent Thus the cellular reaction has more allergic than infective characteristics Heavy eosinophilic infiltration appears to be the hallmark of severe active asthma We observe (as did Cardell 1956) that when death occurs a week or so after the last attack from causes other than asthma the eosinophilia of the bronchi is either absent or so slight that the pathological changes are indistinguishable from those of chronic bronchitis with no history of asthma

We (J C L) have examined partly by serial sections the distribution of thea llergic reactive changes in this series of 25 status deaths and find as have others that the reaction is maximal in the medium and small bronchi An additional observation we have made is that the intensity of the reaction diminishes in the bronchioles and cell infiltration can not be found affecting respiratory bronchioles *(except in one of the cases with emphysema)* Thus the pulmonary parenchyma is unaffected

The findings in cases of clinical bronchitis with destructive centrilobular emphysema (Leopold and Gough 1957) are completely different The inflammatory changes are infective in pattern occur at parenchymal levels cause permanent damage to respiratory bronchioles which develop a destructive emphysema The work at Cardiff therefore suggests that destructive emphysema is not likely to occur in asthma which is uncomplicated by episodes of infective bronchiolitis We would however emphasize that the pathological identification of tissue destructive emphysema is not as easy as would first seem

Heppleston (1953) of Professor Gough s department has confirmed by serial section studies the suggestion of Hartroft (1945) that routine histological sections of the lung can easily be misinterpreted as showing destruction of alveolar walls when none exists and special techniques may be necessary for correct assessment

Wir glauben zum ersten Mal mit Sicherheit nach unseren Beobachtungen aussagen zu können dass die zellularen Reaktionen von den Bronchien und Bronchiolen sich beim nichtkomplizierten Asthma nicht bis in die Endbronchioli fortsetzen

Alle untersuchten Lungen waren erweitert jedoch bei 4 Frauen und 6 Männern waren keine Spuren eines die Alveolen zerstörenden Emphysems zu erkennen

Beweise sind erbracht dass der zerstörende Emphysem selten auftritt wenn nicht eine infektiöse Begleitbronchiolitis vorliegt

RESUMEN

La estadística oficial durante los 8 años transcurridos de 1949 a 1956 indica una cifra de 6 por 100 000 para la mortalidad por asma en Inglaterra y Gales Se presenta la evidencia que justifica la validez de esta cifra El analisis de 101 casos de muerte por status asmaticus en Cardiff muestra que el riesgo de muerte no del todo raro en los niños aumenta notablemente a partir de los 30 años de edad En más de los dos tercios de los casos los pacientes eran de sexo femenino Entre los adultos el 82 % habia padecido asma durante más de 5 años el 61 % durante más de 10 años y el 47 % durante más de 20 años El riesgo es especialmente elevado durante el status asmaticus

Se presentan los resultados obtenidos de la autopsia de 25 adultos (19 mujeres y 6 varones) todos los cuales fallecieron sin duda por asma Se realizaron cortes del pulmón con la tecnica de Gough y Wentworth y cortes seriados de bronquios y bronquiolos El hallazgo caracteristico es una obstruccion generalizada de los bronquios por una espesa capa de mucus gelatinoso conteniendo celulas eosinófilas y una intensa infiltración eosinofilica en las paredes de los mismos Estas modificaciones son máximas en los bronquios medianos y pequeños Una observación sorprendente y aparentemente no registrada con anterioridad es que la reacción celular en el asma no complicado no alcanza a los bronquiolos terminales Los pulmones estaban hiperdilatados en todos los casos pero no se encontro enfisema destructivo en ninguna de las mujeres ni en 4 de los 6 varones Se presentan consideraciones en apoyo de que el enfisema destructivo no aparece en los casos de asma no complicados por episodios infecciosos

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BRONCHIAL ASTHMA IN CHILDREN

by

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With the introduction of the diagnostic tests for allergy sensitization about forty years ago as a means of determining causal factors of asthma and allied conditions now recognized as allergic diseases or syndromes the clinical approach to the study and treatment of these clinical entities in infancy and childhood was placed on a rational basis

The field of allergy especially involving the respiratory system has been developed by the use of physics chemistry and other basic sciences And now psychiatry must be added!

Despite a voluminous literature which contains a vast accumulation of valuable material there still is too much controversy concerning the role that allergenic sensitization actually plays in the direct and contributory etiology and definition of asthma It appears reasonable to assume that a rational clinical approach to this entire subject is necessary if this controversial situation is to be resolved

INCIDENCE

Among chronic ailments in the 170 000 000 people of all ages in the United States allergy ranks third in frequency In the 50 000 000 children in our country allergy in need of treatment occurs in 10 per cent or 5 000 000 children one half of whom have asthma or hay fever or both The majority of children with untreated hay fever contract asthma Asthma is the most common chronic ailment of childhood

DEFINITION SYMPTOMS AND PHYSICAL SIGNS

Why is the term true asthma used by many physicians for children and young subjects? Is it because specific allergenic treatment which often relieves true asthma is ineffective in other conditions associated

with dyspnea Or because dyspnea with bronchitis moist rales may become profuse enough to emit audible sounds which may be mistaken for the dry rales (sibilant and sonorous) noted to cause the characteristic audible wheezing sounds associated with the clinical diagnosis of asthma? The term true asthma may be better understood when the answer to the question What is bronchial asthma? is clarified It appears that the search for causal allergens is largely responsible for considering bronchial asthma and true asthma as synonymous conditions In other words these terms are reserved for only those patients exhibiting hypersensitiveness to allergens Such a point of view is erroneous since the exciting cause may or may not be sensitiveness to allergens (1) In other words asthma *can occur on a nonallergic or nonimmunologic basis Despite the fact that* this form of asthma occurs infrequently in children its recognition is obviously important To distinguish this type of asthma from asthma due to a specific allergic reaction we have coined the term para asthma which will be described separately It should be emphasized that the basic criteria for making a diagnosis of asthma in children at any age rest on a clinical not on laboratory tests Allergy tests are done to determine what causes the asthma not to find out whether a child has asthma

The writer s definition of asthma differs from the orthodox conception in that it is simpler more realistic and more advantageous to speak of an asthma syndrome and the attack of asthma is merely considered as one of the phases of the syndrome Asthma may be broadly defined as a recurring dyspnea usually more marked in expiration associated with wheezing This definition readily lends itself to the recognition of the earlier stages of the disease Asthma can be divided into three district stages

1 *Respiratory oppression* is a subjective symptom complained of only by older children and consists of a sense of tightness in the chest and difficulty in drawing a deep breath No wheezing is present during this stage

2 The *wheezing or preattack stage* is frequently wrongly diagnosed as bronchitis The attack of asthma is absent during this stage This type of asthma with insidious onset is characterized by the appearance of wheezing and dyspnea after repeated attacks of allergic rhinitis or bronchitis They may or may not have direct relation to the season of the year The symptoms in the early stage are not troublesome and during the intervals of remission there may be a cough or some wheezing or complete freedom from symptoms Later typical asthmatic attacks develop These attacks are often preceded by an upper respiratory infection This type is often referred to as asthmatic bronchitis which is misleading since it implies an absence of allergenic sensitization and most of these children belong to the true allergensensitive group Recurrent upper respiratory infection especially in infants triggers the asthmatic symptoms as the primary irritant but it is erroneous to conclude that the infant has a primary bacterial asthma During this stage symptoms are mainly referrable to the variable bronchitic or moist and sibilant and sonorous rales heard in the chest upon auscultation The dyspnea at times may be so mild as to escape attention

3 The *attack stage* represents the peak of the asthma syndrome This type of asthma often starts with acute onset and may last from a few hours to several days The dyspnea is noticeable and trouble some The characteristic posture type of breathing and wheezing respiration heard at 1

distance are typical signs that enable one to diagnose the condition on sight Variable degrees of cyanosis are present If an infection precipitated the attack the mucosa of the nose and pharynx is red and congested If an inhalant substance caused the attack there may be a watery discharge from the nose and the nasal mucosa present the typical pale boggy appearance of allergic rhinitis

The chest examination reveals the breathing to be labored shallow and rapid The shoulders are elevated the suprasternal notch is retracted and expiration is usually prolonged During inspiration the accessory respiratory muscles are straining to the utmost and there is an inward bulging of the lower chest along with a sinking in of the epigastrium

Percussion yields an increase in pulmonary resonance over the entire chest Auscultation reveals shifting sibilant and sonorous rales throughout the entire chest and in the presence of an infection subcrepitant mucous or bubbling rales The normal breath sounds are extremely variable

In children up to two years of age the prominent symptoms of acute asthma may be an alarming increase in the rate of respiration with coughing spasms or troublesome croup and fever

When an attack of asthma persists for more than forty eight hours in spite of repeated injections of epinephrine hydrochloride and other drugs then the attack of asthma is called status asthmaticus

When asthma is protracted over a long period of time despite specific allergy treatment and symptoms are continual or partially or briefly relieved with the aid of various drugs then it is called intractable asthma

In other words status asthmaticus and intractable asthma are exaggerated third stages of asthma the asthma in the former state being acute of relatively short duration and alarmingly severe and in the latter state the asthma is chronic over a prolonged period of time of moderate severity with episodes of superimposed status asthmaticus

LABORATORY AND OTHER DIAGNOSTIC AIDS

All laboratory tests urine sputum blood tuberculin and roentgenoscopy of the chest are routinely performed The presence of eosinophilia in the sputum and blood is a characteristic feature and often is pronounced The incidence of tuberculin reactions in asthmatic children in New York City is comparable to any normal series averaging 25 p 100 There are no roentgenographic findings in the lungs for diagnostic of asthma The X ray of the sinuses may show that an apparently normal maxillary sinus membrane may increase in thickness to a centimeter within a few hours of a sudden attack of asthma (2) The basal metabolism during the free intervals between attacks is usually normal while during the attack it is increased

COMPLICATIONS

Complications of asthma in children as compared to those occurring in the adult are relatively few and are largely chronic hyperplastic sinusitis chronic bronchitis emphysema and chest deformity If asthma is relieved

in children one can expect the lungs to be restored to normal and a considerable reduction even in the chest deformity

It should be stressed that specific hyposensitization treatment cannot cure the complications of asthma

The frequency type and duration of infection with or without fever associated with inclement weather exposure to dampness or cold has some influence on asthma As a rule infection with high fever temporarily clears asthma Recurrent infective rhinitis and bronchitis or both precede the onset of asthma in over 50 percent of the cases and most frequently causes recurrences or aggravation of asthma which is largely a manifestation of allergy because diagnostic skin tests proved them to be sensitive to allergens

Repeated respiratory infections may undermine a child s response to [illegible] treatment [illegible] In the other [illegible] treatment either become less susceptible to respiratory infections or are not adversely affected with asthma during or after the course of the infection

Asthma Associated with Other Allergic Conditions

Hay fever and allergic perennial (vasomotor) rhinitis are the most common allergies associated with asthma The former frequently follows asthma while the latter frequently precedes asthma

In a study of asthma (3) in children ranging in age from six months to fourteen years 20 per cent had a history of eczema commencing during infancy and always preceding the onset of asthma Chronic eczema associated with asthma is troublesome and often difficult to control

Urticaria and angioedema abdominal allergy and occasional migraine do not pose any difficulties

PATHOLOGY

Eosinophilia and edema are the cardinal pathological findings of allergic asthma

Death in uncomplicated cases of asthma may occur in children with *status asthmaticus* in whom the emphysema is pronounced and the bronchi are obstructed by a thick viscid secretion Death also occurs in children with intractable asthma on prolonged corticosteroid therapy because of atrophy of the suprarenal cortex (4) During the last three years the incidence of deaths from asthma in children has increased

DIFFERENTIAL DIAGNOSIS

All types of dyspnea unassociated with wheezing (sibilant and sonorous rales) should not be confused or mistaken for asthma

The recognition of asthma in children should afford no difficulty when one bears in mind that the asthma syndrome takes into consideration the wheezing (preattack) as well as the attack stage that asthma is recurrent

and the dyspnea may be slight or severe The wheezing stage is generally erroneously labelled recurrent or chronic or asthmatic bronchitis which is finally changed to that of asthma when a typical attack occurs During the wheezing and the attack stages asthmatic rales are heard diffusely scattered throughout both lungs During the free interval of symptoms a presumptive diagnosis of asthma can be made from the history of the patient

Asthma can usually be differentiated from congenital stridor laryngismus stridulus retropharyngeal abscess tuberculous tracheobronchial lymph nodes spasmophilia cystic fibrosis of the pancreas and a foreign body in a bronchus

ETIOLOGY

PREDISPOSING FACTORS HEREDITY The important part played by heredity in asthma is generally recognized and the importance of obtaining a reliable family history of allergy cannot be over emphasized During the first five years of life the incidence is about 80 per cent the second five years about 19 per cent and after ten years about 1 per cent (5) These findings apply to children of the allergy sensitive group in which there are positive reactors and negative reactors In cases with bilateral inheritance practically all have their onset before the fifth year (6)

SEX INCIDENCE Twice as many males as females are affected before puberty

AGE OF ONSET OF ASTHMA The onset of asthma is more frequent at one year than at any other age and after the age of ten onset of asthma is relatively uncommon

INFLUENCE OF OTHER DISEASES AND CONDITIONS IN INITIATING THE ONSET OF ASTHMA OR ALTERING ITS COURSE. Pertussis was responsible for initiating the onset of asthma in 15 per cent of the cases measles in 4 per cent scarlet fever in 2 per cent acute pneumonia in 14 per cent and diphtheria and varicella in no cases (7)

The temporary beneficial effect of measles diphtheria acute pneumonia and scarlet fever on the course of asthma may be attributed to the fever accompanying these infectious diseases This is in contrast to the usually unfavorable effect of pertussis on the course of asthma especially during the first two weeks of the infection Varicella does not alter the course of asthma

During the Asian viral influenza of the fall of 1957 Falliers et al (8) observed an overall lowered incidence of asthma during the acute phase of the epidemic followed by a considerably greater number of asthmatic attacks four to eight weeks later

Acute rhinitis and bronchitis were discussed in the chapter on Complications

Chronic suppurative sinusitis occurs rarely as a primary cause of asthma and as a secondary factor in only 2 per cent

Chronic bronchitis with or without emphysema implies a secondary infection of the bronchial mucosa and exerts an unfavorable influence on the course of asthma Most of the patients who are nonreactors of the allergen sensitive group have varying degrees of chronic bronchitis

Enlarged or diseased tonsils and adenoids rarely operate as etiological factors in asthma Surgical intervention initiated the onset of asthma in

3 per cent of the cases and in others may adversely affect the course of asthma

Other Contributing Factors Physical overexertion indiscretion in diet especially the eating of ice cream and the drinking of iced liquids variations in weather sudden fall in barometric pressure the change of seasons exposure to cold winds and sudden changes in temperature pungent fumes gases or odors and freshly painted rooms are important contributory factors in inducing asthmatic attacks

Specific Factors The diagnosis once made the physician proceeds to search for the specific allergens responsible for the asthma To depend on the allergy sensitization tests alone would lead one astray Therefore the procedure to employ in a search for the etiologic basis of asthma involves in addition to sensitization tests a carefully detailed history and a thorough physical examination employing roentgen rays tuberculin tests laboratory and other diagno tic aids

The history is the first and one of the most important steps in determing causal factors of asthma The history has a direct and significant bearing on the interpretation of the skin tests and the form of therapy to be instituted Because no form of test procedure can cover all possibilities all available methods of testing should be used with due regard for the safety of the

[illegible]

a child with allergies (positive reactor) who may or may not have active clinical allergic symptoms Such a person may have causal or noncausal sensitization In the latter instance sensitization may be either a past or a potential factor of allergy A child with a negative reaction with active clinical symptoms from the corresponding allergen is called a negative reactor Sensitizations are usually multiple and are more frequently encountered in children than in adults Food sensitizations with any method of testing is discovered more readily in children than in adults Often the offending food has to be determined by test diet when the skin tests are negative (9)

Nonreactors who have been treated with pollen mold dust or other inhalant extracts with the average doses at the upper limit usually used for the positive skin reacting patients will invariably fail to be relieved of their symptoms *The need for larger doses of specific allergenic extracts is the* final goal of treatment for protection in the skin refractory group of cases

With the recognition of the pitfalls of allergy testing it is at times possible to take appropriate steps to avoid or minimize their occurrence and thereby protect the patient

ETIOLOGIC CLASSIFICATION

In this classification there are two main groups which are inclusive of all types of asthma

1 Allergen Sensitive Asthma (Immunological)

A Positive Test Reactors

B Negative Test Reactors

- Nonallergen Sensitive Asthma (Non immunological Paraasthma) In a large series of cases 98 per cent were classified as allergen sensitive asthma and 2 per cent as nonallergen sensitive asthma (10)

ALLERGEN SENSITIVE ASTHMA

The substances that are known to be etiologic factors in asthma are as follows pollen molds dust animal emanations orris insecticides and other inhalants food bacteria drugs and biologicals and therapeutic animal sera

The paths of absorption of the allergens may be the respiratory gastro intestinal skin and parenteral routes or by absorption from a focus

It is obviously clear that in the successful management of asthma in children it is important to differentiate between etiologic and nonetiologic allergenic sensitization This applies equally to the positive and negative test reactors who can be classified into the following four groups

1 The allergen proved to be the sole current etiologic factor of asthma

2 The allergen acting as one of various causes of asthma—primary or contributory

3 The allergen shown to be a past but not a current etiologic factor because of freedom from exposure or ingestion etc

4 The allergen playing no part in the past or present etiology and referred to as a potential factor of asthma

Inhalant Allergens Ninety eight percent of allergic patients are sensitive to one or more substances of the inhalant group

The most common sensitizations are pollen dust feathers animal emanations and molds

A survey (11) made a decade ago of a series of children with allergic symptoms showed pollen to be either the sole major or minor contributory cause of symptoms in 64 per cent of the cases thus marking pollen as the most common single cause of allergy During the last decade there has been an apparent increase in the incidence The incidence in the United States and Canada is higher than it is in other countries largely because we have three distinct pollen seasons with the fall pollen season particularly of the ragweed type possessing an index of sensitization higher than the pollens of the trees (spring) or grasses (summer) Moreover the more toxic pollens of the fall season are almost exclusively reserved for the North American Continent When the symptoms are confined to the nose the term hay fever is used and when the bronchial tubes are involved pollen asthma Asthma occurs as a complication in about 60 per cent of the pollen sensitive children The majority of children with pollen allergy who are refractory to the skin tests suffer from pollen asthma with or without hay fever In other words only a small number of patients with uncomplicated hay fever show the phenomena of negative skin tests to pollen

House dust sensitization is one of the most common reactions encountered but as an etiologic factor of asthma at least in children it is not as great as reports in the literature would lead one to believe It is usually associated with sensitivity to other allergens but may occur independently

Sensitization to feathers Sensitization reactions to duck goose and chicken feathers are the most common and seem to play mostly a contributory role in asthma

Sensitization to horse dander by test is becoming progressively less common Sensitization to cats is more frequent than any other household pet and its dander is more toxic than dog dander

The remaining inhalant sensitizations almost always occur in conjunction with one or more of the more important inhalant substances

As a general rule inhalants play a minor part in causing allergic symptoms during the first year of life

Food Allergens All children older than two years with positive skin reactions to foods also react positively to one or more inhalant substances while the reverse is not true

Sensitization to bacterial allergens in asthma was first described by Walker (12) However in children the whole question of bacterial hyper sensitization and its relation to infection in asthma is indeed a complex problem It has not as yet been solved by the methods of skin testing employed at present It cannot be denied that bacterial infection of the bronchial mucosa and upper respiratory tract plays an important role in many children with asthma allergen sensitive positive and negative reactors

With all other causal factors eliminated the clue to the diagnosis of bacterial asthma in a child can be based only on the information derived from a detailed history and repeated clinical observations of the cause and effect of infections on the asthmatic state About 18 per cent of the children make up this group now classified under the allergen sensitive nonreacting group for obvious reasons All of these patients have varying degrees of chronic bronchitis and the relationship between attacks of asthma and infections is quite pronounced

Sensitization to drugs in children in recent years has been on the increase Aspirin and penicillin sensitivity are the most common

Sensitization to molds resulting in asthma was first stressed by van Leeuwen (13) and later by Feinberg (14) among others The latter reported an incidence with the scratch technic with his molds of 40 per cent and states that such as positive reaction almost invariably denotes clinical allergy to molds The most common offender is Alternaria

2 NONALLERGEN SENSITIVE ASTHMA (PARA ASTHMA NONIMMUNOLOGIC)

From the point of view of etiology and the pathologic conditions found in these children which have a direct bearing on the etiology they must be differentiated from the main group These cases are caused directly by an enlarged thymus by enlarged bronchial lymph nodes (tuberculous and nontuberculous) by atelectasis of a portion or of an entire lung or by any pathologic condition inducing tracheobronchial stenosis or interference with lung function In other words a child with paraasthma manifests clinical signs and symptoms of asthma plus the pathologic condition causing it The children have a positive family history of allergy and are inherently asthmatic in type

Paraasthma usually occurs within the first two years of life and the characteristic findings are the gradual onset of asthmatic symptoms with only brief periods of remission from symptoms The chest reveals the usual signs of asthma and the roentgenograms in the majority of cases confirm the presence of the pathologic condition causing the partial or

complete bronchial stenosis or interference with normal lung function In the final analysis parasthma is bronchial asthma but the exciting cause is not an allergen

TREATMENT

The treatment of asthma may be discussed as follows

1 *The treatment of the acute attack* Epinephrine hydrochloride injected hypodermically is the most effective drug Inhalation of a nebulized mist of epinephrine (1 100 solution) in glycerin or 1 200 solution of isopropyl epinephrin (Aleudrine or Pafadrin in European literature and Aludrine Isonorin and Isuprel in the United States) is effective

Ephedrin sulfate is used orally in mild cases Aminophylline is especially useful with a severe asthma The intravenous injection slowly given often brings prompt relief Ephedrin with aminophylline and phenobarbital is the most common combination used orally Codeine and potassium iodide is used for cough

Antibiotics and sulfonamide drugs or both should be orally administered at the beginning of an infection

The antihistamine drugs unfortunately continue to be commonly used for asthma in older children despite their ineffectiveness However in my experience antihistamines in adequate doses are indicated for asthma in infants without respiratory infection It is now realized that these drugs have their limitations in hay fever and they do not have the power to hyposensitize the patient against the offending pollen

The corticosteroids alleviate but do not cure asthma However at times they may be life saving and as adjunctive agents have a definite place in the management of asthma provided their limitations and harmful effects are clearly understood and respected

The inhalation of detergent mixtures has not proven satisfactory

The injection of morphine should not be employed Deaths have been known to follow this form of narcosis Tranquilizing drugs are safe

Hospitalization which affords a change of environment frequently is the only measure necessary for the relief of *status asthmaticus* in children Owing to dehydration many children require a continuous slow intravenous drip using up to one liter of a 5 to 10 per cent solution of glucose in distilled water Caffeine sodium benzoate may be injected subcutaneously every 4 to 5 hours during the acute emergency

2 *The treatment of the asthmatic patient by specific or nonspecific measures or both and other measures* The ideal treatment is the removal of the [illegible]

effective for a majority of children

Sensitivity to food is best treated by complete restriction of the offending foods from the diet for a period of a least one to two years Cooking may so alter or denature many foods as to render them harmless whereas the raw or partially cooked foods cause symptoms

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their own homes 80 per cent continued to be free from asthma or to have only an occasional spell of wheezing We have learned that parentectomy for the intractable asthmatic child can be successfully performed and is a rational procedure for the rehabilitation of the total child However we have not yet uncovered the basic mechanism responsible for the recovery

Outgrowing Asthma In a certain number of children outgrowing asthma does actually occur Statistics on this phase of asthma are not available Because of the phenomenon of outgrowing asthma, children who are given the benefit of rational modern therapy overcome their asthma much sooner and more satisfactorily than those who are consigned to the fate of merely outgrowing their affliction The danger of replacing early appropriate treatment with that of waiting and hoping lies in the fact that meantime serious complications may supervene and thereby considerably diminish the chances the child has of becoming relieved of asthma. In the light of our present knowledge every effort should be made [illegible] matter how lengthy

Results of Treatment Appropriate treatment relieves asthma in many instances for life yet recurrences are common and investigation into and treatment of its causes again bring about freedom from symptoms Allergic diseases are essentially chronic diseases In many instances observation over extended periods of time with repeated courses of treatment is frequently necessary before complete relief can be accomplished It can be conservatively estimated that abou 80 per cent of the children are either entirely or markedly relieved of asthma as a result of proper modern therapy

SUMMARY

There are 50 000 000 children in the United States Ten per cent or 5 000 000 children have allergy in need of treatment one half of whom have asthma or hay fever or both The majority of children with untreated hay fever contract asthma Asthma is the most common chronic ailment of children

Asthma may be broadly defined as dyspnea with wheezing It may occur in acute attacks or it may persist more or less all the time with wheezing as the predominant symptom and when triggered by acute respiratory infection it then is often called asthmatic bronchitis

When an attack of asthma persists for more than forty eight hours refractory to the use of epinephrine hydrochloride and other drugs the attack is referred to as Status Asthmaticus When asthma is protracted and remains severe over a long period of time despite appropriate modern treatment it is referred to as Intractable Asthma.

The history is the first and one of the most important steps in determining

causal factors of asthma The history has a direct and significant bearing on the interpretation of the skin tests and the form of therapy to be instituted All available methods of testing should be used with due regard for the safety of the patient in the search for causal allergens A positive skin reaction to an allergen reveals a child with allergies (positive reactor) who may or may not have active clinical allergic symptoms

Nonreactors who have been treated with pollen or other inhalants extracts with the average doses at the upper limit usually used for the positive skin reacting patients will invariably fail to be relieved of their symptoms The need for larger doses of specific allergenic extracts is the final goal of treatment for protection in the skin refractory group of cases

With the recognition of the pitfalls of allergy testing it is at times possible to take appropriate steps to avoid or minimize their occurrence and thereby protect the patient

Repeated respiratory infections may undermine a child s response to hyposensitization treatment to the extent that not only does the treatment fail to afford relief from asthma but may at times aggravate it On the other hand the larger group of children receiving hyposentitization treatment either become less susceptible to respiratory infections or are not adversely affected with asthma during the course of the infection

During the last three years the incidence of deaths from asthma in children has increased Eosinophilia and edema are the cardinal pathological findings of allergic asthma

The ideal treatment is separation of the patient from the offending substance From a practical standpoint this is not always feasible The simplest and effective procedure is to desensitize (hyposensitize) the patient The offending food is removed from the diet

Often additional therapeutic agents termed nonspecific are used and at best offer temporary relief

The removal of tonsils and adenoids does not relieve asthma except in a few instances and then the relief is only temporary Elective operations should not be performed during the pollen seasons

The injection of allergenic extracts during the poliomyelitis season is not contraindicated

The antihistamine drugs for asthma are effective in infants and ineffective in older children

The corticoid steroids alleviate but do not cure asthma However their limitations and harmful effects should be clearly understood and respected

The commonly accepted drugs used to control bronchitis wheezing spells and acute attacks of asthma are too well known for discussion here

The children should be protected in their home environment from sensitizing substances known to cause asthma and hay fever

The younger the patient and the sooner specific allergic treatment is begun the better are the prospects for controlling the asthmatic condition Replacing early appropriate treatment with that of waiting for the child to outgrow the asthma leads to the danger of serious chronic complications and considerably diminishes the chances of ultimate relief About 80 per cent of the children respond favorably to allergy treatment

Emotional disturbances may play an important and distressing role in

children with asthma About 10 per cent of all asthmatic children fail to respond to appropriate modern treatment in their own community These children are the intractable asthmatics with various personality disorders and they often hold on to their crippling illness for reasons largely related to their human rather than physical environment

The humane and most dependable therapeutic measure to break effectively the vicious circle of physical and emotional suffering in a child with intractable asthma is parentectomy removal of the child from his human environment to a home or institution where a warm emotional climate is provided by sympathetic mother and father figures Here relief from asthma sometimes occurring dramatically within a few hours or days gives the child courage to take a new lease on life Here his personality emerges and develops slowly into mature ways These observations were made at the nonsectarian Jewish National Home for Asthmatic Children at Denver Colorado where this type of child receives medical psychologic sociologic educational and domicillary care

Follow up studies on 150 children who have returned to their own homes after an average absence of two years revealed that 90 per cent remained well while away from home One or more years after they returned to their own homes 80 per cent continued to be free from asthma or to have only an occasional spell of wheezing Parentectomy for the intractable asthmatic child can be successfully performed and is a rational procedure for the rehabilitation of the total child

RÉSUMÉ

Il y a cinquante millions d enfants aux États Unis Dix pour cent d entre eux soit cinq millions d enfants sont atteints de maladies allergiques necessitant des soins medicaux La moitie de ces enfants souffrent d asthme de rhume des foins ou des deux a la fois

La plupart des enfants atteints de rhume des foins et n etant pas traites contractent l asthme

Pour dépeindre l asthme a larges traits on peut le designer comme une dyspnée accompagnee de sifflements respiratoires

L asthme peut survenir sous forme de crises aigues ou il peut etre de duree plus ou moins longue la respiration sifflante etant le symptome le plus marquant lorsque l asthme est déclenché par une infection respiratoire aigue on l appelle frequemment « asthme bronchitique »

Quand une attaque d asthme dure plus de quarante huit heures et resiste a l administration de chlorhydrate d adrenaline et d autres medicaments cette forme de la maladie est dénommée « etat de mal asthmatique »

Lorsque malgre un traitement moderne approprie l asthme se prolonge et reste grave on le designe sous le nom d « asthme invétere »

L historique de la maladie est un des elements primordiaux pour pouvoir déterminer les causes de l asthme Cet historique a une importance directe et significative pour l interpretation des tests cutanes et le choix du traitement

Pour la recherche des allergenes en cause toutes les methodes de tests

ne doivent etre employees qu avec les precautions necessaires pour la securite du malade

Une reaction cutanee positive a un allergene démontre chez un enfant l existence d un état d allergie (reacteur positif) qu il présente ou ne presente pas de symptomes cliniques actifs d allergie Les « non réacteurs » traites avec des pollens ou d autres extraits d inhalants (comme on les utilise géneralement pour les tests cutanés) a des doses moyennes allant jusqu a la limite *superieure ne verront jamais disparaitre par ce moyen* leurs symptomes pathologiques

Des doses plus fortes d allergenes specifiques sont necessaires pour obtenir la protection des malades appartenant au groupe des « non reactifs »

La connaissance des surprises que peuvent reserver les tests de l allergie permet parfois de faire le nécessaire pour qu elles se produisent le plus rarement possible et ainsi de proteger le malade

Des infections respiratoires répétées peuvent diminuer la reaction d un enfant au traitement de desensibilisation si bien que non seulement il n apporte aucun soulagement a l asthme mais peut encore aggraver la maladie Par ailleurs des groupes nombreux d enfants traités par la desensibilisation deviennent moins receptifs aux infections respiratoires ou bien ne sont plus atteints d asthme au cours de ces infections

Au cours des trois dernieres annees le taux de la mortalité par l asthme a augmente parmi les enfants Dans l asthme allergique l éosinophilie et l œdème bronchique sont des constatations primordiales

Le traitement ideal serait de separer le malade de l allergene nocif En pratique cela n est pas toujours realisable La methode la plus simple et la plus efficace est la desensibilisation (hypo sensibilisation) du malade On supprime du régime alimentaire les aliments nocifs Souvent l adjonction à *bon escient d autres agents therapeutiques dits non spécifiques* procurent au malade un soulagement temporaire

L ablation des amygdales et des vegetations adenoides n atténue l asthme que dans des cas exceptionnels encore s agit il que d un soulagement temporaire Les opér itions O R L ne doivent pas etre pratiquées pendant les saisons polliniques

Il n y a pas de contre indication aux injections d extraits d allergenes pendant la saison de la poliomyelite

Les médicaments antihistaminiques agissent sur les enfants en bas age mais pas sur les enfants plus ages

Les cortico steroides attenuent l asthme mais ne le guerissent pas Cependant il faut bien connaitre les limitations et les dangers qu ils présentent et en tenir compte

Les remedes habituellement employés contre la bronchite les sifflements respiratoires et les crises aigues d asthme sont trop connus pour qu il en soit discute ici

Les chances de dominer l asthme sont d autant meilleures que le malade est plus jeune et que le traitement specifique de l etat allergique a pu commencer plus tot Si au lieu de traiter a temps d une maniere appropriée l enfant on attend de le voir « sortir en grandissant » de la maladie il existe un danger de voir s installer de sérieuses complications chroniques et les chances de guerisons sont considerablement diminuées

Environ 80 % des enfants réagissent favorablement aux traitements allergiques

Les troubles emotifs peuvent exercer une influence importante et aggravante sur l asthme des enfants Environ 10 % des enfants asthmatiques ne reagissent pas aux traitements modernes et appropries quand ils se trouvent dans leur milieu familial Ces enfants sont des cas d asthme rebelle qui s accompagnent de diverses maladies de la personnalité resultant beaucoup plus de leur entourage que de leur condition physique

Le traitement le plus sur et le plus humain pour ces enfants atteints d asthme rebelle est de briser le cercle vicieux de leurs souffrances physiques et psychiques en pratiquant la « parentectomie Nous voulons dire par la que l enfant doit etre retiré de son entourage social et transfere dans un foyer ou une institution ou il retrouvera un climat affectif chaleureux et familial Dans ce nouveau climat l amelioration de l asthme survient parfois avec une rapidité spectaculaire en quelques heures ou quelques jours et l enfant reprenant courage « signe un nouveau bail » avec la vie Sa personnalité se fait jour et se développe lentement jusqu à sa maturité

Ces observations ont eté faites au Home National Israélite pour les enfants asthmatiques a Denver (Colorado) U S A Dans cette institution non confessionnelle les enfants reçoivent des soins medicaux psychologiques sociaux il y est pourvu a leur vie « familiale » et à leur éducation

Nous avons étudié les cas de 150 enfants retournés dans leurs familles apres des absences d une durée moyenne de deux ans Cette etude nous a montré que 90 % de ces enfants étaient restés libres d asthme pendant la période ou ils etaient absents de chez eux Un an ou plusieurs années apres leur retour dans leurs familles 80 % continuaient a etre libérés de leur asthme et n avaient qu occasionnellement des crises de sifflements respiratoires

Pour les cas d asthme rebelle des enfants la « parentectomie » peut etre pratiquee avec succes c est la un moyen rationnel de parvenir au retablissement total tant physique que moral de l enfant

ZUSAMMENFASSUNG

Es gibt 50 000 000 Kinder in den Vereinigten Staaten 10 Prozent oder 5 000 000 Kinder haben behandlungsnotwendige Allergien die Halfte hat Asthma Heufieber oder beides zugleich Die meisten Kinder mit unbehandeltem Heufieber bekommen auch Asthma Asthma ist das am meisten verbreitete chronische Leiden von Kindern

Asthma kann ganz allgemein als mit Keuchen einhergehende Dyspnoe definiert werden Es kann in akuten Attacken auftreten oder mehr oder weniger die ganze Zeit mit Keuchen als vorherrschendem Symptom bestehen bleiben wenn es von einer akuten Respirationsinfektion uberlagert wird dann wird es oft asthmatische Bronchitis genannt

Wenn eine Asthmaattacke langer als 48 Stunden gegen Epinephrin hydrochlorid und anderen Medikamenten refraktar bleibt so wird diese Attacke als Status Asthmaticus bezeichnet Wenn Asthma protrahiert verlauft und uber eine langere Zeit trotz geeigneter moderner Behandlung

schwer bleibt, dann wird es ungebandigtes Asthma (intractable Asthma) genannt

Die Anamnese ist die erste und eine der wichtigsten Handlungen um die Kausalfaktoren des Asthma aufzudecken Die Anamnese hat direkten und bedeutsamen Bezug zur Auslegung der Hautteste und auf die zu verordnende Behandlungsmethodik Beim Forschen nach Kausalallergenen sollen fur die Gesundheit des Patienten alle gultigen Testmethoden verwendet werden Eine positive Hautreaktion einem Allergen gegenuber zeigt ein Kind mit Allergien auf (positiv Reagierender) das aktive klinische Allergiesymptome haben kann oder auch nicht

Nicht Reagierende die mit oberen Dosisdurchschnittswerten wie sie gewohnlich fur im Hauttest positiv reagierenden Patienten verwendet wurden von Pollen und anderen Inhalationsstoff extrakten behandelt wurden werden unveranderlich ihre Symptome beibehalten Die Verwendung grosserer Dosen von spezifischen Allergenextrakten ist das Endziel der Behandlung zum Schutz der

Mit dem Bekanntwerden der

geworden geeignete Massnahm

oder ihr Auftreten zu verringern und dadurch den Patienten zu schutzen Wiederholte Infektionen der Atemwege konnen die Antwortsreaktion des Kindes der Desensibilisierung gegenuber solchermassen untergraben dass die Behandlung nicht nur Asthma nicht zum Verschwinden bringt sondern es mit der Zeit noch verschlimmert Andererseits wird der Grossteil der mittels einer Desensibilisierung behandelten Kindern entweder weniger empfanglich fur Respirationsinfektionen oder er wird nicht von erschwerenden Asthmaanfallen wahrend des Infektionsverlaufes befallen

Wahrend der letzten drei Jahre hat die Asthmasterblichkeit bei Kindern zugenommen Eosinophilie und Ödem sind die hauptsachlichen pathologischen Zeichen fur allergisches Asthma

Die Idealbehandlung ist die Trennung des Patienten von der krankheitsauslosenden Substanz In der Praxis ist dies aber nicht immer durch

verwendet und bedingen im besten Falle ein zeitweiliges Freisein von Symptomen

Tonsillektomie und Entfernung der Rachenmandeln kupiert Asthma nicht ausgenommen einige wenige Falle und in denen ist die anfallsfreie Zeit nur vorubergehend Aufschiebbare Operationen sollen in der Pollensaison nicht durchgefuhrt werden

Wahrend der Poliomyelitissaison ist die Injektion von allergenen Extrakten nicht kontraindiziert

Antihistaminpraparate sind in der ersten Kindheit wirksam bei alteren Kindern hingegen aber nicht

Die corticostereoiden Stoffe erleichtern Asthma heilen es aber nicht Jedoch sollen ihre Anwendungsbegrenzungen und schadlichen Wirkungen bekannt sein und respektiert werden

Die gewohnlich bei Bronchitis Keuchen und akuter Asthmaattacke angewandten Medikamente sind zu gut bekannt um hier naher darauf einzugehen

Die Kinder sollen in ihrer hauslichen Umgebung vor Asthma und Heufieber erzeugenden sensibilisierenden Substanzen geschutzt werden Je junger der Patient und je fruher mit der spezifischen Allergiebehand lung begonnen wird um so besser sind die Aussichten Asthma unter die Kontrolle zu bekommen Wenn man die geeignete Fruhbehandlung mit dem Warten des Kindes auf das sogenannte dem Asthma entwachsen vertauschen will so erzeugt man damit eine Gefahr von ernsthaften chro nischen Komplikationen und vermindert die Chance einer entgultigen Heilung betrachtlich Ueber 80 % der Kinder sprechen auf Allergiebehand lung gunstig an

Emotionelle Storungen konnen bei Kindern mit Asthma eine wichtige und ernsthafte Rolle spielen Ueber 10 % aller asthmatischen Kinder sprechen in ihrer gewohnlichen Umgebung auf eine geeignete moderne Behandlung nicht an Diese Kinder sind die ungebandigten Asthma tiker mit verschiedenen Personlichkeitsstorungen und sie behalten ihre verkruppelnde Krankheit aus Grunden die mehr in Verbindung mit ihrer menschlichen als mit ihrer physikalischen Umwelt stehen

Die humane und wirkungsvollste therapeutische Massnahme um den *circulus vitiosus* von physischen und emotionellen Leiden bei einem an ungebandigtem Asthma erkrankten Kinde sicher zu durchbrechen ist die Entfernung von den Eltern (Parentectomy) die Entfernung des Kindes von seiner menschlichen Umgebung und Aufnahme in ein Heim oder eine Institution wo ein freundliches emotionelles Klima von sympa thischen die Vater und Mutterstelle vertretenden Leuten geschaffen wird Hier tritt Heilung vom Asthma manchmal schon effektvoll innerhalb einiger Stunden oder Tage auf was dem Kind den Mut zu neuem Leben gibt Diese Beobachtungen wurden in dem keiner Sekte angehorigen Jewish National Home fur asthmatische Kinder in Denver Colorado gemacht wo diese Art von Kindern medizinische psychologische soziolo gische erzieherische und hausliche Fursorge erhielten

Studien an 150 Kindern die nach einer durschnittlichen Abwesenheit von 2 Jahren nach Hause zuruckkehrten zeigten dass 90 % sich wahrend *ihrer Abwesenheit wohl befanden Ein bis zwei Jahre nach ihrer Ruckkehr* in die Familien blieben 80 % weiterhin frei von Asthma oder hatten nur sporadisch Keuchenfalle Parentektomie kann fur das Kind mit einem ungebandigtem Asthma erfolgreich durchgefuhrt werden und ist eine rationelle Massnahme um die Person des Kindes wieder voll und ganz herzustellen

RESUMEN

Hay 50 millones de ninos en los Estados Unidos de Norte America de los cuales el 10 % es decir 5 millones padecen alguna forma de alergia que requiere tratamiento medico La mitad de esos alergicos tiene asma o fiebre de heno o ambos La mayoria de los ninos con fiebre de heno no tratada llega a presentar asma El asma es la enfermedad cronica infantil mas frecuente

El asma puede ser definido de manera general como una disnea con sibilancias Puede presentarse como episodios agudos o puede ser mas o menos permanente con las sibilancias como sintoma caracteristico y

cuando se agrava con una infeccion respiratoria aguda es llamado a menudo «bronquitis asmática»

Cuando un ataque de asma persiste durante mas de 48 horas y no cede al tratamiento con clorhidrato de epinefrina u otras drogas similares recibe el nombre de «status asmaticus» Cuando continua y permanece severo durante largos períodos a pesar de tratamientos modernos y adecuados se lo denomina «asma intratable»

La historia clínica es el primer paso y el mas importante para establecer la etiología del asma y es por otra parte fundamental para interpretar correctamente las prudebas cutáneas y decidir la terapeutica a utilizar Todos los metodos disponibles de testificacion practicados con las precauciones debidas deben ser ensayados para localizar al alergeno responsable Una reaccion positiva indica un niño con alergias (reactivo) que puede presentar o no síntomas alergicos clínicos activos

En los pacientes que no presentan sensibilidad cutánea (no reactivos) el tratamiento con extractos de polen o inhalantes en las dosis usuales invariablemente fracasa En estos casos la proteccion se alcanza solamente cuando se utilizan dosis mayores que las necesarias para los pacientes reactivos

El conocimiento de los riesgos de la testificación permite a veces tomar las medidas necesarias para eliminarlo o disminuirlo protegiendo por lo tanto al paciente

Las infecciones respiratorias a repetición pueden llegar a modificar la respuesta del paciente a tal punto que el tratamiento hiposensibilizante no solamente resulta inactivo sino que a veces agrava la sintomatología Por otra parte la mayoria de los ninos tratados se hace menos susceptible a las infecciones respiratorias o son menos afectados por el asma en el transcurso de las mismas

La incidencia de la mortalidad infantil por asma ha aumentado en los ultimos tres anos Las características patológicas principales en el asma alergico son la eosinifilia y el edema

El tratamiento ideal es la eliminacion de la sustancia causal lo cual no siempre es realizable prácticamente El procedimiento mas simple y efectivo consiste en desensibilizar (hiposensibilizar) al paciente Si se trata de un alimento se lo elimina de la dieta

Diversos agentes terapéuticos llamados no específicos son utilizados a menudo y en el mejor de los casos sólo producen una mejoria pasajera

La extraccion de las amigdalas y vegetaciones no mejora el asma, a excepcion de unos pocos casos en que la mejoria es solo temporaria Deben *evitarse las operaciones otorrinolaringologicas durante la estacion polinica*

La inyeccion de extractos alergénicos durante la epoca poliomielitica no esta contraindicada

Los antihistamínicos son efectivos en los niños de corta edad e inefectivos en los mas grandes

Los corticoides alivian pero no curan el asma No obstante debe tenerse muy en cuenta sus limitaciones y efectos nocivos

Las drogas de uso corriente en las bronquitis y asma son bien conocidas y no seran discutidas

Los ninos deben ser protegidos en el ambiente familiar de las sustancias sensibilizantes reconocidas *como causantes de asma y fiebre de heno*

Las perspectivas de una mejoría son mayores cuanto más joven sea el paciente y cuanto mas pronto se comience el tratamiento específico La actitud de esperar que el niño evolucione favorablemente al crecer disminuye considerablemente la probabilidad de una mejoria y puede conducir a serias complicaciones crónicas Aproximadamente el 80 % de los niños responde favorablemente al tratamiento alergico

Los trastornos emocionales pueden desempeñar un papel importante y enojoso en los niños asmáticos Mas o menos el 10 % de los niños es refractario al tratamiento llevado a cabo en su propio medio Estos niños constituyen el grupo de asmáticos intratables con diferentes trastornos de su personalidad y a menudo la causa de su enfermedad reside en el ambiente humano que los rodea mas que en el ambiente fisico

La medida terapéutica mas humanitaria y mas segura para quebrar el circulo vicioso de sufrimiento fisico y emocional de un niño con asma intratable es la «padrectomía» es decir el alejamiento del nino del ambiente familiar en alguna institución donde encuentre un cariñoso y simpático clima emocional En estos casos la mejoría del asma que a veces se presenta dramaticamente en unas pocas horas o días confiere al niño el valor necesario para poder tomar un nuevo impulso en su vida Su personalidad emerge y se desarrolla lentamente de una manera mas madura Estas observaciones han sido efectuadas en la Jewish National Home for Asthmatic Children organización no sectaria en Denver Colorado donde este tipo de niños recibe atención médica psicológica sociológica educativa y familiar

Observaciones sobre 150 niños que volvieron a sus hogares luego de una ausencia media de dos años indican que el 90 % estuvo libre de síntomas durante el alejamiento Uno o mas anos despues de la vuelta el 80 % continuaba libre de asma o tenía solamente trastornos leves y esporadicos En el caso de los niños asmáticos intratables la padrectomia» es un procedimiento racional para la total rehabilitacion del paciente y puede ser aplicada con resultados satisfactorios

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SYMPOSIUM II

Propriétés physico-chimiques des anticorps

Physico-chemical properties of allergic antibodies

Physiko-chemische Eigenschaften der Antikorper

Propriedades fisico-quimicas de los anticuerpos



INTRODUCTION

by

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There are few subjects as intriguing to the allergist as the nature and significance of antibodies It is therefore with great anticipation that we look forward to hearing the presentations of the various members of this symposium all of whom are recognized experts in this complex field A brief review of the subject in relation to diseases of hypersensitivity will serve as a point of departure for the more detailed and advanced views which are to follow

Of all the various properties ascribed to known different antibodies there are three which are common to all These are (1) that they are protein in nature (2) there is an increased production following exposure to antigen and (3) they have an affinity for the specific antigen It is generally held that antibodies are normal gamma globulins with a particular immune specificity According to the template theory they possess an alteration in configuration which is complementary to the antigen as a consequence of being synthesized in relation to an antigen template They are said to differ from each other only by a small difference in configuration at the reactive site There is some difference of opinion regarding this concept and it has been suggested that different antibodies probably arise from different cell types

The reticulo endothelial system lymphocyte and plasma cell are thought to be involved in the production of gamma globulin and antibody It seems reasonably clear that the plasma cell is the ultimate source of the finished product and this will be elucidated by Dr Dixon who has done much work on the problem Gamma globulin has been demonstrated in [illegible]

that such patients not only may have resistance to certain viral infections but also may develope allergic manifestations with skin sensitizing antibody demonstrable by skin testing It is probable that many of these cases represent a marked hypogammaglobulinemia rather than a complete

absence of this protein since relatively minute quantities of skin sensitizing antibody are required for skin testing

The definition of the plasma proteins is a difficult procedure and must be interpreted with care For example gamma globulin in terms of electro phoretic mobility is probably made up of many diverse forms of protein When serum is analysed by ultracentrifugation the proteins separate out in a different manner since the method depends both on the size and shape of the various moieties In addition to an albumen and a globulin peak both of which account for approximately 97 p 100 of the total protein a small fraction of heavy or macromolecules of the S 19 variety separates out as well This small fraction which is derived from the beta and gamma globulins has assumed considerable interest in recent years for it has been shown to contain a number of important antibodies These include the isoagglutinins the latex or agglutinating factor useful in the diagnosis of rheumatoid arthritis, the antibody to thyroid which is found in Hashimotos disease and as will be described by Dr Sehon skin sensitizing antibody It is of interest that blocking antibody does not reside in this fraction Clearly then as methods of detection improve the definition of antibody must be related to the method used and undoubtedly present concepts will be altered

There are a number of classifications of antibodies Those which occur without any obvious antigenic stimulation are termed natural antibodies as compared to acquired antibodies which arise only after exposure to a known antigen

At least two other forms of antibody are of importance in allergy These are humoral and cellular The former consist of a variety of different types of which precipitating and non precipitating are two chief forms So called precipitating antibody is believed to be necessary for most patterns of animal hypersensitivity such as anaphylaxis the Arthus phenomenon and the lesions of vasculitis This antibody will form a precipitate in the test tube when antigen is added will fix complement is heat stable and does not occur unless antigenic stimulation is provided Because skin sensitizing antibody does not possess these properties and is found in man without obvious prior antigenic stimulation it was given the name reagin and thought to be a very different substance as compared to classical anti body This concept is under considerable scrutiny since it is now possible to demonstrate combination of antigen and skin sensitizing antibody *in vitro* In addition the evidence that injection of a foreign protein such as diphtheria toxin in man may give rise not only to precipitins but also to skin sensitizing antibody both of which may be demonstrated by conventional means and both of which will neutralize toxin suggests that these two types of antibody must be closely related This aspect of the problem as well as the significance of blocking antibody will be considered by Dr Sherman Dr Sehon as well as Dr Kabat

Resistance to infection and allergy or hypersensitivity are related to the same basic mechanism and the essential difference between the two states has so far remained an enigma One of the most dramatic of the body reactions to invasion by foreign organisms be they bacterial viral or para sitic is the formation of antibody with a specific affinity for some part of the *invading organism* While this is undoubtedly a defense mechanism

on the part of the host it is the same series of events which in certain circumstances gives rise to hypersensitivity or allergy

The importance of antibody as a factor in the production of allergic disease is based on the premise that an antigen antibody complex is formed which in turn produces the various symptoms which may be observed It is well known however that in many of the clinical states of man which have been accepted as being allergic in nature antibody cannot be demonstrated with existing methods Not only is this true for the more complex diseases such as those involving connective tissue but it also holds for some of the more common forms of allergy such as certain cases of asthma and rhinitis Take for example those patients in whom either asthma or skin and joint manifestations may be induced by the administration of penicillin or the sulpha compounds In some of the former positive skin tests may be eluciditated both by the direct as well as the indirect method of passive transfer but in a fair percentage no such antibody can be demonstrated Another example is the allergic individual who developes an infection followed or accompanied by asthma rhinitis or not infrequently urticaria What kind of antibody is involved in these cases of undoubted bacterial allergy?

There is the opposite state of affairs in those individuals who come of an allergic background with large quantities of skin sensitizing antibody demonstrable both by direct and indirect means but who are devoid af all clinical manifestations even when exposed to the specific antigen excepting for the skin reaction What then is the precise significance of skin sensitizing antibody? While the answer to this question is unknown at present it is possible as has often been postulated that tissue or fixed antibody may be of marked importance but this has not as yet been demonstrated for the skin sensitizing type of antibody It is also probable that some metabolic alteration is responsible for the difference between the clinically aller

demonstrated by Dr Chase and will be considered by him later in this symposium Here too there are some interesting questions for it has been shown that in animals sensitized to tuberculin tissue sensitivity may exist in the absence of skin sensitivity

Because of the morphological changes which are observed in the various disease entities grouped under the haeding of collagen or connective tissue diseases and the fact that in many such patients numerous allergic manifestations may precede the onset they have been thought to depend on an antigen antibody mechanism While time does not permit a detailed review of the nature of so called autoantibodies it is now clear that some such mechanism must play a role Thus the production of such lesions as vasculitis carditis and nephritis by the injection of a large dose of foreign serum or the induction of lesions of the central nervous system and other tissues by the use of homologous tissue in Freunds adjuvants or a similar medium is well established Indirect evidence for the existence of antibody in the form of gamma globulin has been provided by the application of the Coons fluorescein labelling technique to many tissues obtained by biopsy or necropsy from patients with a variety of clinical syndromes including

rheumatic fever glomerulonephritis polyarteritis DLE and amyloiditis to mention but a few It should be emphasized however that this is indirect evidence since the demonstration of gamma globulin in a lesion is not incontrovertable evidence that it is antibody with a specificity for the tissue in which it is found Thus gamma globulin may also be found in joint lesions induced by trauma However as investigation advances it is becoming more obvious that the gamma globulin identified in these lesions is indeed antibody particularly in those experimental lesions associated with circulating antibody and more specifically in the lesions of thyroiditis (Hashimotos disease) and other diseases related to the production of auto antibodies It might be pointed out here that certain of the normal tissue proteins are foreign to the individual in whom they reside in that they do not come into contact with the circulation under normal circumstances

In concluding these somewhat rambling remarks it may be well to point out that one of the chief difficulties in the investigation of antibody systems is the nature of antigens the vast majority of which are impure It is not surprising therefore that the resultant antibody should also be impure in the sense that it may apparently possess several different qualities or indeed may consist of different antibodies each with a specifity to some component of the complex antigen This aspect of the problem will be dealt with by Dr Kabat and Dr Grabar

SUMMARY

The subject of antibodies is of paramount importance to the allergist since the manifestations of allergy are related to combination of antigen with antibody Many problems exist such as the complexities of antigens the source of antibody and tis relation to cell types such as lymphocyte and plasma cells We are thus to hear about more advanced techniques regarding the isolation of both humoral and cellular antibodies their location in cells tissues and plasma proteins and the significance of these *relative to allergic mechanisms Techniques used such as electrophoresis* and ultracentrifugation have provided newer concepts and pointed up differences between naturally occurring antibodies and those which occur as a consequence of antigenic stimulation The interpretation of such results musts be made with care in relation to the method used Thus gamma globulin is probably made up of many different protein complexes Similarly most antigens or allergens are quite complex substances and may as a result give rise to multiple antibody responses The more recent and significant advances in this field will be presented and discussed by the members of this symposium all of whom are internationally recognized experts in this field

RÉSUMÉ

La question des anticorps presente un interet capital pour l allergologiste du fait que les manifestations de l allergie sont liées a la combinaison d un antigene avec un anticorps

De nombreux problemes se posent tels que la complexité des antigenes les sources productrices d anticorps et leurs rapports avec les cellules de types divers telles que les lymphocytes et les plasmocytes

Nous allons entendre des exposes sur les techniques les plus perfectionnees concernant l isolement des anticorps humoraux et cellulaires la détermination de leur location dans les cellules les tissus et les proteines du plasma et la signification de ces données pour l interpretation des mecanismes de l allergie

L emploi des techniques telles que l electrophorese et l ultra centrifugation ont donné naissance a de nouveaux concepts et permis de reconnaitre les differences qui existent entre les anticorps spontanes et ceux qui se reproduisent sous l influence stimulatrice d un antigene L interpretation des résultats obtenus doit etre faite avec circonspection et soin en tenant compte des procedes employes

Ainsi la gamma globuline est elle constituee par plusieurs complexes protéiniques differents De meme la plupart des allergenes ou antigenes sont des substances essentiellement complexes leur administration peut determiner plusieurs types d anticorps

Les progres les plus recents et les plus interessants realises dans ce domaine seront présentes par des conférenciers qui sont tous d une renommee mondiale dans ce domaine

ZUSAMMENFASSUNG

Das Gebiet der Antikorper ist fur die Allergieforscher von grosster Bedeutung seitdem man die allergischen Manifestationen auf eine Antikorper Antigenreaktion zuruckfuhrt Es bestehen viele Probleme wie die Komplexizitat der Antigene die Herkunft der Antikorper und die Beziehungen zu Zelltypen wie den Lymphozyten und Plasmazellen Wir mussen so fortschrittlichere Techniken finden Techniken hinsichtlich der Isolierung von humoralen und zellularen Antikorpern ihrer Lokalisation in den Zellen Geweben und Plasmaproteinen und deren Bedeutung fur die Allergie Mechanismen Techniken wie die Elektrophorese und die Ultrazentrifuge fuhrten zu neueren Anschauungen und liessen Unterschiede zwischen den naturlichen Antikorpern und jenen die nach einer Antigenstimulierung auftreten erkennen Die Interpretierung solcher Resultate muss immer die dabei verwendete Methode berucksichtigen So scheinen die Gamma Globuline aus vielen verschiedenen Protein Komplexen zu bestehen Die meisten Antigene und Allergene sind ebenso ganz complexe Substanzen und konnen so viele Antikorper Antwortsreaktionen bedingen Die neuesten und wichtigsten Fortschritte auf diesem Gebiet werden von den Teilnehmern dieses Symposiums prasentiert und diskutiert werden von Teilnehmern die alle auf diesem Forschungsgebiet international bekannte Experten sind

RESUMEN

El *tema de los anticuerpos es de importancia fundamental para el alergista* puesto que las manifestaciones alergicas estan vinculadas a la combinación entre antígenos y anticuerpos Existen infinidad de problemas tales como la complejidad de los antígenos el origen de los anticuerpos y su relación con los diferentes tipos de células tales como linfocitos y células plasmáticas Es de esperar, por lo tanto el desarrollo de tecnicas nuevas y mejores en lo que respecta a la purificacion de anticuerpos humorales y celulares y su caracterización entre las proteinas del plama células y tejidos y su vinculación con los mecanismos alérgicos Las tecnicas usadas actualmente como electroforesis y ultracentrifugación han originado nuevos conceptos y han establecido diferencias entre los anticuerpos naturales y los que se forman como consecuencia de la estimulación antigenica La interpretación de estos resultados debe hacerse con mucho cuidado y teniendo en cuenta el método utilizado Asi por ejemplo muchos complejos proteínicos entran en la composición de la gama globulina De la misma manera la mayoría de los antigenos o alergenos son sustancias muy complejas y producen como consecuencia anticuerpos diferentes El autor presenta los ultimos y mas importantes resultados en este campo para ser discutidos por los participantes de este symposium todos los cuales son expertos reconocidos

SKIN SENSITIZING AND BLOCKING ANTIBODIES

by

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The first evidence that the blood of allergic patients contains a substance capable of producing passive sensitization was offered by Ramirez (1) in 1919 He reported the case of a previously non allergic patient with pernicious anemia who was transfused with blood from a donor sensitive to horses There was no reaction at the time but several days later when the recipient rode in a horse drawn vehicle he had asthma This pheno menon of passive general sensitization by transfusion has been studied in greater detail by Loveless (2) and others They showed that when blood from a person with hayfever is transfused into a non sensitive person the sensitizing substance disappears from the circulating blood in a few hours to become fixed in the skin and mucosae where its presence is manifested by positive skin and conjunctival tests which persist for weeks

The more familiar phenomenon of local passive sensitization was des cribed by Prausnitz and Kustner (3) in 1921 They showed that injection of a small amount of serum from an allergic patient into the skin of a non allergic person produced a localized sensitization with the same character and specificity as that manifested by skin tests upon the allergic individual

Sera of a large proportion of atopic patients showing well marked imme diate type skin reactions to intracutaneous tests with antigen will produce this phenomenon in the skin of most normal persons The practical

an indirect method of skin

well known

reagin to the active prin ciple of such sera because of doubt as to its relationship to previously known antibodies At the time the reagin was believed to be limited to the human species and to result from hereditary influences The importance of contact with the antigen in causing its developement was not then established Subsequant studies have shown that antibodies with the same capacity to produce the Prausnitz Kustner reaction may be induced in persons without any apparent hereditary tendency to allergy by injections of horse serum or ascaris antigen Antibodies with the same property have been found in spontaneously sensitive dogs and cattle and experimentally induced in rabbits and guinea pigs by injecting ovalbumin (6) For these

reasons the general descriptive term skin sensitizing antibody appears preferable to atopic reagin '

From the transfusion experiments described it is inferred that the skin sensitizing antibody is present in the skin and mucosae of allergic persons and gives rise to clinical symptoms and skin reactions Bradel has shown that nasal polyps of allergic persons contain skin sensitizing antibodies in concentrations 40 times more that in their sera (7) Attempts to recover such antibodies from skin have not been successful

The passive sensitization produced by intracutaneous injection of allergic serum is sharply localized to the site of injection and persists for several weeks suggesting the antibody has a strong affinity for the skin With a small amount of antigen no reaction will be obtained if the test injection misses the original site by as little as one or two centimeters This requires great care in marking the sensitized sites but has the advantage that the passive nature of any sensitization elicited may be proved by a control test in an untreated area of the skin While the antibody remains strictly localized antigens spread freely in the non allergic person and injection of a sufficiently large amount of antigen (usually in the range of 0 2 mgm of antigen nitrogen) elsewhere in the body will produce a reaction in the sensitized site

In the case of sera highly sensitive to certain foods such as egg fish or nuts the same reaction may occur if the specific food is eaten by the passively sensitized subject (8) Wheals produced by such systemic exposure to antigen are rarely more then 2 3 cms in diameter suggesting that this is the limit of spread of antibody in the skin

The visible reaction observed apparently results from the effects on the blood vessels of the skin produced by histamine liberated from a bound form by the antigen antibody reaction The liberation of histamine from human allergic blood and tissues by antigen is readily demonstrated in vitro (9 10) The possible implication of other intermediaries such as 5 hydroxy tryptamine and acetyl choline cannot be completely excluded but the marked inhibition of the reaction by large doses of antihistamine drugs suggests that histamine is the principal factor

This rather complex biological reaction is in general an exceedingly sensitive indicator of the antigen antibody reaction a site made with a active anti castor bean serum reacting to as little 3×10^{-5} micrograms of antigen nitrogen However the intensity of the observed reaction may be influenced by the amount of tissue bound histamine and by the reactivity of the blood vessels to free histamine both of which may vary in different normal individuals Experimentally it may be shown that exhaustion of bound histamine by a previous injection of 48/80 inhibits the subsequent reactions to antigen A temporary local refractory state may also be produced by previous stimulation of the site with free histamine (11)

These biologic variables are reflected in the differences of reaction of apparently normal skins Thus when dilutions of the same highly potent anti castor bean serum were injected into 5 receptive individuals one reacted to a titre of 1 100 two to 1 1000 and two to 1 10 000 (12) It is apparent that *such dilution titres* do not accurately indicate the absolute amount of antibody in the serum However they can be used to compare two sera in the same test subject at the same time

Within limits the threshold of reaction appears to depend on the product of concentrations of antigen and antibody in the site Thus if undiluted serum reacts with 3×10^{-5} micrograms of antigen nitrogen the 1 10 dilution will react to approximately 3×10^{-4} and 1 100 with approximately 3×10^{-3} However a dilution is soon reached which will not react with even 1 0 microgram There is no apparent prozone and no point of optimal proportions

The reaction with antigen uses up a certain amount of antibody and after a sufficiently strong reaction the site will no longer react to the same antigen This specific neutralization is permanent in contrast to the non specific refractory state produced by stimulation of the site with histamine which lasts a few days

Successive tests on the skin site are not an exact method of demonstrating neutralization of antibody since that small volume of antigen injected may not reach all parts of the sensitized areza

If the sensitizing serum is mixed with antigen before injection into the skin site neutralization takes place at once Thus if portions of the same serum mixed with differing amounts of antigen are used to prepare a series of sites subsequent testing with an excess of antigen reveals a sharp point of neutralization (12) This neutralization test is of value in the study of blocking antibodies to be discussed later

By definition the Prausnitz Kustner reaction is the method of demonstrating the skin sensitizing antibody However because of the biologic and technical problems of using human skin as an indicator many attempts have been made to find some other test which can be related to its presence Sera of hayfever patients containing the skin sensitizing antibody do not give precipitin reactions or produce passive anaphylaxis in the guinea pig Sera of persons artificially sensitized to horse serum and containing skin sensitizing antibodies often show both of these properties but sera of persons spontaneously sensitive to horse serum which are equally active in skin sensitization do not

When skin sensitizing antibodies are experimentally induced in rabbits by injections of antigen precipitins are also formed but there is no quantitative correlation between the two properties of the serum Artificially induced skin sensitizing antibodies in guinea pig sera are usually associated with anaphylactic antibodies but again there is no quantitative correlation (6)

Sera of some untreated atopic persons cause agglutination of red cells coated with the specific antigen but no technique yet devised gives results paralleling the Prausnitz Kustner reaction The same may be said of the complement fixation reaction

The addition of specific antigen to the whole blood of naturally allergic persons causes a release of histamine from the blood cells into the plasma (9) Middleton Van Arsdel and I (13) have attempted to sensitize normal blood *in vitro* by the addition of plasma of allergic patients and then release histamine by addition of antigen Although this passive sensitization has been successful in some cases the results are variable As yet there is no *in vitro* method of determining the skin sensitizing antibody

One of the best known characteristics of the skin sensitizing antibody is its thermolability Sensitizing activity of serum is destroyed by heating at 56°C for one to four hours and is not restored by the addition of comple

ment This property enables us to separate blocking from skin sensitizing antibodies (14) However it is not a unique property of skin sensitizing antibodies since human precipitins may also be destroyed by heat and rabbit skin sensitizing antibodies are not

A more unusual property is the failure of the human skin sensitizing antibody to pass through the placenta from mother to fetus Guinea pig anaphylactic antibodies and essentially all human antibodies that have been studied readily pass from the maternal to the fetal circulation The impermeability of the human placenta to skin sensitizing antibody was reported by Bell and Erickson (15) and has been confirmed in the Roosevelt Hospital laboratories (16) In many of the same cases hemagglutinins typhoid agglutinins and diphtheria antitoxin were shown to be transmitted

While it is well known that most antibodies are gamma globulins the chemical nature of the skin sensitizing antibody is less easily established By the older methods of salt fractionation it was found to be included in *the pseudoglobulin Vaughan and associates (17) applied Cohn s method* of alcohol *fractionation to allergic sera* The *skin sensitizing activity* was not limited to any one fraction but was greater in fraction III d which consists chiefly of beta globulin

Attempts to correlate skin sensitizing activity with electrophoretic fractions of the serum proteins have given confusing results Newell (18) by Tiselius electrophoresis found it to be in the gamma globulin Using convection electrophoresis Loveless and Cann (19) found activity to be related to beta globulin while Campbell and Cann (20) thought it might by related to alpha 2 Sehon and Rose (21) used starch electrophoresis and found the activity mainly in gamma globulin Menzel and Cooke (31) after applying a variety of electrophoretic and chemical methods report that it cannot be fixed in any one component and suggest that it differs from classical antibodies by complexing with various protein components of the serum

It has been noted that skin sensitizing antibodies (associated with precipitins) may be induced in humans by injections of horse serum and in rabbits and guinea pigs by injections of ovalbumin In general the injection of pollen antigens into non allergic persons does not produce skin sensitizing antibody Evidence of the relation of inhalation of pollen to develepement of this antibody is indirect While patients predisposed by heredity may become sensitized to only a few of the many pollens to which they are exposed sensitization is never found to pollens whose geographic distribution precludes the possibility of exposure

After sensitization is established further exposure to the pollen antigen by the injection treatment of hayfever usually produces a 3 fold to 10 fold increase in the titre of antibody during the first 2 or 3 months of treatment (22) Obviou ly this is not desensitization such as is possible in anaphylaxis Treatment of longer periods of time may be accompanied by a drop in the antibody titre to or below its original level

In some cases when a patient sensitive to two pollens is treated with only one it is found that the titre of reaction to both pollens increases proportionately (22) This suggests the possibility that the same antibody may react with both pollens but further evidence would be needed to establish the point

When a hayfever patient is treated with injections of pollen extract and the serum is repeatedly studied by the dilution and neutralization tests both of which might be expected to indicate the amount of sensitizing antibody the titres of the two tests do not change proportionately This suggests that both the amount and the kind of antibody have changed as a result of injection treatment Cooke and associates (23) attributed this change to the developement of a blocking antibody distinct from the sensitizing antibody and competing with it for antigen More direct evidence of the developement of blocking antibody was offered by Loveless who showed that blocking antibody was thermostable and remained active when the skin sensitizing antibody was destroyed by heating serum at 56 °C (14)

The presence of blocking antibody in such heated sera can be demonstrated in several ways The most direct is simply to mix the heated serum and a normal control serum
the two series in tests on sen
evidenced by decreased re
results are usually obtained in tests on passively sensitized sites than in naturally sensitive skin since the amount of sensitizing antibody reacting with the antigen is fixed In working with ragweed pollen this direct method often gives confusing results since the ragweed pollen extract contains several different antigens which are not all equally effective in stimulating formation of blocking antibody in the treated patient By this test blocking antibody can be demonstrated only if it inhibits all of the ragweed antigens to which the site is sensitized (22)

The most commonly used method depends upon inhibition of the neutralization test by blocking antibody Mixtures of a sensitive serum and various dilutions of antigen suitable for determining the neutralization point are set up in triplicate To one series are added aliquots of the heated blocking serum to the others heated serum of an untreated hayfever patient and heated normal serum (14)

The end point in the series containing serum of the untreated hayfever patient is the same as with normal serum indicating the absence of blocking antibody before treatment The neutralization point in the series containing serum of the treated patient is raised presumably because some of the antigen is bound by blocking antibody and cannot take part in the neutralization

The blocking antibody does not form a visible precipitate with antigen but if sensitive techniques are used sera containing blocking antibody fairly consistently cause agglutination of red cells coated with antigen Like the skin sensitizing antibody it does not passively sensitise guinea pigs and does not fix measureable amounts of complement

In many other properties blocking antibody resembles the ordinary artificially stimulated antibodies rather than the naturally acquired skin sensitizing antibody It shows less affinity for tissues than the skin sensitizing antibody and diffuses out an intracutaneous site within a day or two Development of blocking antibody is readily induced in non allergic persons b
those use
antibody

Like most other human antibodies it readily passes through the placenta from maternal fetal circulation (16) Unlike the skin sensitizing antibody which developes as a result of inhaling a multitude of antigens the blocking antibody shows the strict specificity typical of antibodies induced by injections of antigen

Hampton Bukantz and associates (25 26) have shown that the precipitation of ragweed antigen and rabbit anti ragweed serum is partially inhibited by the addition of blocking serum from a treated hayfever patient Portnoy and Sherman (27) found that human era containing blocking antibody for ragweed pollen specificially inhibited the fixation of complement by ragweed antigen and rabbit anti ragweed serum while sera of untreated ragweed sensitive patients containing only skin sensitizing antibody did not This complement fixation inhibition test permits the detection of blocking antibody without the Prausnitz Kustner procedure and so relates it to the more familiar immunologic reactions However since it is less sensitive than the passive transfer method it is not a satisfactory substitute for routine use

Since the development of blocking antibody is the principal immunologic change produced by successful injection treatment of hayfever and this antibody appears to bind the antigen when mixed with it it is quite logical to assume that it represents the actual mechanism of protection of the treated patient

There is good evidence that the ability of the patient to tolerate pregressively larger injections of pollen extract is correlated with the developement of blocking antibody which protects against general reactions This is illustrated by the findings in 13 cases of ragweed hayfever six of whom were sensitive only to fraction I of the pollen and 7 to both fraction I and II All developed blocking antibody for fraction I but only one developed blocking antibody for fraction II Those who developed blocking antibody for the fractions to which they were sensitive tolerated large doses of extract without reactions while those who were allergic to both fractions but developed blocking antibody only for fraction I had more reactions despite the fact that their top doses were lower (22)

General reactions occur when the antigen spreads through the blood stream from the site of injection to various shock organs During this passage through the blood stream the blocking antibody has ample opportunity to combine with and inactivate the antigen In clinical hayfever on the other hand the pollen reaches the shock organ directly and there is some question how effectively the blocking antibody demonstrated in the plasma but not yet in the tissues can protect

This is illustrated by the method which Maunsell (28) used for determining blocking antibody She took serum from the patient and mixed it with pollen antigen in various dilutions Comparable control mixtures containing the same amounts of antigen in saline were made and the two compared in tests on the patient s own skin The difference in the reaction produced by [illegible]
the presence [illegible]
was capable [illegible]
blocking antibody in the blood stream of the patient did not prevent the skin reaction when antigen saline mixtures were injected The situation

may be similar when pollen grains fall on the sensitized nasal mucosa

Loveless (29) Alexander (30) and others have studied the relationship between the clinical results obtained in the treatment of hayfever and the titres of blocking antibody developed with conflicting results No clear correlation has been established between the clinical and immunologic findings The blocking antibody may be the protective factor but conclusive proof depends upon more accurate and objective methods of measuring the therapeutic results in hayfever

SUMMARY

The skin sensitizing antibody is demonstraded in the sera of allergic patients by the Prausnitz Kustner phenomenon of passive transfer No other method gives reliable evidence of its presence

This antibody shows a striking affinity for the tissues When injected into the blood stream it rapidly becomes fixed in the skin and mucosae where it persists for as long as two months When injected intracutaneously it remains fixed at the site of injection for several weeks

The skin sensitizing antibody is neutralized by reaction with adequate amounts of antigen so that no further reaction is elicited by antigen

This antibody is destroyed by heating serum at 58° C and activity is not restored by complement Unlike most antibodies it does not pass through the placenta Chemically it has not been clearly linked with any one of the electrophoretic components of serum

The blocking antibody is found in the sera of allergic patients only after treatment with injections of antigen It does not act as a precipitin but may cause agglutination of antigen coated red cells It can be demonstrated by its ability to inhibit the fixation of complement by the specific antigen and rabbit antisera

This antibody does not sensitize skin nor show the marked affinity for tissues of the skin sensitizing antibody It is thermostable at 56° C This permits separation from sensitizing antibody The blocking antibody passes through the placenta and moves in electrophoresis with the gamma globulin

The development of blocking antibody appears to be related to the increased tolerance for injected antigen during treatment Its relationship to clinical protection against hayfever is less clearly proven

RÉSUMÉ

L observation du phenomene de transfert passif de Prausnitz Kustner permet d etablir la presence d un *anticorps sensibilisateur de la peau* dans le serum des sujets allergiques

Il n existe pas d autre methode pour prouver de façon plus certaine la présence de tels anticorps

Ces anticorps témoignent d une remarquable affinite pour les tissus Injectes dans la circulation sanguine ils se fixent rapidement sur la peau

et sur les muqueuses ou ils restent pendant une durée de temps allant jusqu à deux mois

Quand ils sont injectés par voie intradermique ils demeurent fixés dans le derme au lieu de l injection pendant plusieurs semaines

L anticorps sensibilisateur de la peau est neutralisé par une quantité appropriée d antigene de telle sorte que l antigene ne provoque plus de reaction ultérieure Cet anticorps est détruit quand le sérum est chauffe à 58° et le complement ne lui rend pas son pouvoir actif A la difference de la plupart des anticorps celui ci ne traverse pas le placenta

Chimiquement il a ete clairement rattaché a n importe lequel des composants electrophoretiques du serum

L anticorps bloquant est forme dans le serum sanguin des malades allergiques apres injection repétees d antigene Il ne se comporte pas comme une précipitine mais peut provoquer l agglutination des globules rouges enrobes d antigene Sa presence peut etre demontree par sa propriété d inhiber la fixation du complément par l antigene specifique et par des anti serum de lapin

Cet anticorps (bloquant) ne sensibilise pas la peau et n a pas pour les tissus l affinité marquée de l anticorps sensibilisateur reaginique Il est thermostable a 56° ce qui permet de le separer de l anticorps sensibilisateur

L anticorps bloquant semble conditionner l accroissement de la tolerance de l antigene lors du traitement de désensibilisation

Son incidence sur la protection clinique contre le rhume des foins est moins nettement prouvee

ZUSAMMENFASSUNG

Die Beobachtung des Phanomens der passiven Uebertragung nach Prausnitz Kustner gestattet in der Haut allergischer Personen die Anwesenheit eines hautsensibilisierenden Antikorpers festzustellen

Es existiert keine andere Methode die Anwesenheit dieses Antikorpers mit Gewissheit nachzuweisen

Dieser Antikorper zeigt eine bemerkenswerte Affinitat zu den Geweben Wenn er in den Blutkreislauf injiziert wird so bindet er sich sehr rasch in der Haut und den Schleimhauten wo er bis zu 2 Monate bleibt

Wenn er subkutan injiziert wurde so bleibt er in der Epidermis am Ort der Injektion wahrend mehrerer Wochen fixiert

Der hautsensibilisierende Antikorper wird durch seine Reaktion mit einer passenden Antigenmenge neutralisiert und zwar auf diese Weise dass das Antigen keine spateren Reaktionen mehr auslost

Dieser Antikorper wird zerstort wenn man das Serum auf 56° C erhitzt und das Komplement gibt ihm die aktive Fahigkeit nicht wieder Zum Unterschied zu den meisten Antikorpern kann er die Plazenta nicht durchschreiten

Chemisch wurde er nicht mit gewissen elektrophoretischen Komponenten des Serums in Verbindung gebracht

Nur nach einer Behandlung mittels Antigeninjektionen findet man im Serum allergischer Patienten *blockierende Antikorper* vor Seine Aktion

ist nicht die des Präzipitins aber er kann die Agglutination von Antigen beladenen roten Blutkorperchen auslosen Seine Anwesenheit kann mittels seiner Fahigkeit die Komplementbindung durch das spezifische Antigen und dem Kaninchenantiserum zu verhindern nachgewiesen werden

Dieser blockierende Antikorper sensibilisiert die Haut nicht und besitzt nicht die markante Gewebsaffinität des hautsensibilisierenden Antikorpers Er ist bei 56° C thermostabil was seine Trennung vom sensibilisierenden Antikorper gestattet

Der blockierende Antikorper geht durch die Plazenta durch und folgt in der Elektrophorese den Gamma Globulinen

Die Bildung des blockierenden Antikorpers scheint mit der gesteigerten Toleranz dem im Verlaufe der Behandlung injizierten Antigen gegenuber zusammen zu hangen

Sein Einfluss auf einen klinichen Schutz gegenuber dem Heuschnupfen ist nur ungenau bewiesen

RESUMEN

La existencia en el suero de los enfermos alergicos del anticuerpo sensibilizante de la piel se pone de manifesto por la prueba de transferencia pasiva de Prausnitz Kustner no existiendo ningun otro método valedero Este anticuerpo presenta una afinidad notable por los tejidos Cuando se lo inyecta por vía intravenosa se fija rapidamente en la piel y las mucosas donde persiste hasta dos meses si se lo inyecta por via intracutánea permanece varias semanas fijado en el sitio mismo de la inyección El anticuerpo sensibilizante puede ser neutralizado por el antigeno en cantidades adecuedas es destruido por calentamiento a 58 y su actividad no aparece nuevamente por el agregado de complemento a diferencia de la mayoria de los anticuerpos es incapaz de atravesar la placenta quimicamente se lo ha encontrado en todos los componentes electroforeticamente diferentes del suero

El anticuerpo bloqueante aparece solamente despues del tratamiento con inyecciones de antigeno No es precipitante pero puede provocar la aglutinación de glóbulos rojos sensibizados con el correspondiente antigeno y ademas inhibe la fijacion del complemento por el sistema anticuerpo de conejo antigeno específico Este anticuerpo bloqueante no sensibiliza la piel ni se fija en los tejidos es termoestable a 56° lo que permite su separacion del anticuerpo sensibilizante atraviesa la placenta y migra electroforeticemente con las gama globulinas El aumento de anticuerpo bloqueante parece estar vinculado con la mayor tolerancia al antigeno inyectado durante el tratamiento Su relacion con la mejoria clínica de la fiebre de heno no esta claramente demostrada

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PROBLEMS IN THE STUDY OF ALLERGIC ANTIBODIES

by

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There are many problems in the study of antibodies responsible for various allergic reactions which are being intensively studied and many of these will be considered at this Congress However I wish to discuss two problems each of which illustrates some of the difficulties and pitfalls in applying immunochemical technics to allergy but at the same time has much to offer to those who will thoroughly explore all possibilities and consider with especial care the limitations of the materials with which we must all necessarily work

The first problem is the nature of the antibody which has the capacity to induce the typical wheal and erythema in human skin Individuals suffering from spontaneous allergies of the immediate type such as hay fever and urticarias frequently contain an antibody in their serum which can passively transfer this wheal and erythema type of skin sensitivity to normal subjects—the Prausnitz Kustner reaction (1)—and it is this capacity which suggests that an antibody is responsible for the manifestations of hypersensitivity Unfortunately however the Prausnitz Kustner reaction is the only reliable procedure for detecting this kind of antibody All efforts to demonstrate it by any of the usual *in vitro* serological reactions have failed There are several possibilities to explain these failures any of which may be true First the antibody may be a classical type of antibody but occurring usually in such small concentrations that amounts which can produce a Prausnitz Kustner reaction are far below the levels which can be detected by any of the usual *in vitro* reactions such as precipitation complement fixation etc Secondly the antibody may be intrinsically unique in character so that it would combine with antigen without forming a precipitate etc even if present in amounts comparable to those in the usual types of precipitating sera There is no basis currently available to permit a choice between these alternatives and efforts to attribute the skin sensitizing properties of certain antibodies to a non precipitating variety of antibody have been subject to various criticisms These derive essentially from inability

to measure the amount of skin sensitizing antibody quantitatively and failure to exclude the presence of antibodies to impurities in the sera used

Attempts to study the properties of skin sensitizing antibodies are based upon earlier quantitative studies on systemic anaphylaxis (2 3) passive cutaneous anaphylaxis (4) and the Arthus reaction (5) which using precipitating antisera to well defined purified but not pure antigens provided an estimate of the quantities of antibody needed to produce these various types of allergic reactions these findings are well known to all of you Moreover it was possible by serial addition of small amounts of antigen as described by Heidelberger and Kendall (6 cf 7) selectively to leave in the supernatant the so called non precipitating or co precipitating variety of antibody and it could be demonstrated that this variety of antibody was also equally potent per unit weight in producing systemic (8) anaphylaxis as was the antibody in the original serum It could produce passive cutaneous (9) anaphylaxis but was unable to produce an Arthus reaction (5) Antibody with lower aggregating capacity also showed less capacity to fix complement (10) More recently Weigle and Maurer (11) have shown that the non precipitating type of antibody can actually precipitate if complement is present The important point to remember is that all of these studies were carried out by actual injection of known quantities of antibody nitrogen using sera from different individual animals and with various antigens and have been confirmed in many laboratories these data are not seriously affected by the presence of small amounts of antibody to impurity

It had been known that some rabbit antisera possessed the power to sensitize human skin passively so that a typical wheal and erythema reaction would occur on injection of antigen into the site 24 hours later This antibody showed many of the characteristics of that occurring in human sera from patients with spontaneous allergies and it seemed reasonable to try to determine the relation of the skin sensitizing property of these rabbit antisera to the antibodies present Rabbit antisera to crystalline egg albumin were studied It was at first inferred that the skin sensitizing properties of the antiserum were due to non precipitating anti egg albumin (12) However it was known that only a proportion of the rabbits injected with crystalline egg albumin produced antisera with skin sensitizing properties for human skin The others though frequently containing substantial quantities of anti egg albumin did not possess this property (12)

A detailed reinvestigation of this problem by Dr John H Vaughan in this laboratory (13) showed that the anti egg albumin itself either as the mixture of

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rable number of sera which did sensitize skin showed that in some instances a better wheal and erythema reaction was obtained with egg white conalbumin or ovomucoid than with crystalline egg albumin In other instances a better wheal and erythema reaction was obtained with egg white than with crystalline egg albumin crystalline conalbumin or ovomucoid All the anti egg albumin sera studied contained small amounts of antibody to other antigens present as trace impurities in the crystalline egg albumin used for immunization Antibodies found included anti conalbumin

anti-ovomucoid and anti lysozyme Antibody to an unidentified antigen which gave a very slow band in agar diffusion (14) was identified by Dr Marie Kaminski (15) using immunoelectrophoresis (16 17) as probably antibody to the β_1 egg globulin Anti β_2 egg globulin was also present (15) Skin

in the rabbit to certain antigens have the capacity to sensitize human skin whereas antibodies to the major identified proteins obtainable from purified egg proteins do not The nature of the antigens which do give rise to skin sensitizing antibodies may shed light on the kinds of substances to which skin sensitivity readily develops The results of this study tell us nothing about the properties of skin sensitizing antibodies themselves whether they are intrinsically non precipitating or whether if obtainable in adequate concentration, they would show *in vitro* reactions More important however, the findings show the dangers in assuming that antisera contain antibody only to a single antigen no matter how pure it is thought to be Each antiserum must be examined by as many technics as possible—agar diffusion immunoelectrophoresis quantitative precipitin studies etc to establish the presence of impurities and their amounts if possible Even this is not conclusive since failure to detect antibodies to impurities by a given set of technics does not preclude their being found as soon as a more sensitive technic is introduced

The same kind of difficulty was encountered *but unfortunately not recognized* by Kuhns and Pappenheimer (18) in their studies on Schick negative humans immunized anamnestically with diphtheria toxoid One individual so stimulated produced a non precipitating variety of diphtheria antitoxin and his serum had the capacity to induce sensitivity of the wheal and erythema type on injection into Schick positive individuals Other persons studied by Kuhns (19) produced non precipitating antitoxin which did not induce skin sensitivity Kuhns and Pappenheimer (18 19 20) at first postulated two and then three varieties of diphtheria antitoxin—precipitating non skin sensitizing non precipitating skin sensitizing and non precipitating non skin sensitizing It was first thought that anamnestic stimulation with purified diphtheria toxoid would induce only the production of antitoxin and their interpretation rested heavily upon this assumption More recent studies by Kuhns and Dukstein (21) have shown that 11 of 53 subjects produced antibodies to one or more antigens other than antitoxin Using a more sensitive and somewhat more flexible agar diffusion method described by Oakley and Fulthorpe (22) as modified by Preer (23) Dr Irving Finger and I (24) were able to detect in 8 out of 8 sera from Schick negative individuals immunized with the same Massachusetts State Laboratory toxoid used by Kuhns and Pappenheimer at least one and as many as five antibodies other than antitoxin these antibodies were estimated to comprise at least 15 percent of the total antibody While Kuhns and Dukstein (21) found antibody to impurities only in those individuals with very high antitoxin levels the antitoxin in the 8 individuals studied in our series was in the usual range There is little doubt that with the preparations used antibody to impurities can be found in almost all individuals Preparations of crystalline toxin prepared by Pope (25) and

the highly purified products of Relyveld *et al* (26) have not yet been studied Moreover the serum which was furnished by Dr Pappenheimer from Hu the individual reported to contain skin sensitizing non precipitating antitoxin was found by Dr Finger (24) to contain precipitating antibody to an impurity other than antitoxin The antitoxin itself was of the non precipitating variety The antibody to impurity was detectable by the Preer technic even though the sample of serum studied had declined in antitoxin content from 80 to 10 units per ml Most of the correlations adduced by Kuhns and Pappenheimer (18) and by Kuhns (19) to establish the association between skin sensitivity and non precipitating antitoxin were based on biological testing which is not capable of the precision necessary to prove their point in the presence of antibody to impurities It must once again be inferred that probably one or more antigens contaminating diphtheria toxoid may well be capable of stimulating skin sensitivity and that the nature of these antigens and the reason for their production of this kind of sensitivity is as yet unknown

The second major problem I should like to consider is the subject of the various polysaccharides notably the pneumococcal polysaccharides dextrans and levans which are antigenic in man and which stimulate the production of precipitins and skin sensitizing antibodies of the wheal and erythema type These seem not to have received much attention from allergists

In 1929 Tillett and Francis (27) reported that patients convalescent from pneumococcal lobar pneumonia showed a positive immediate skin reaction of the wheal and erythema type when tested with the specific capsular polysaccharide of the type of pneumococcus causing the disease and not with the specific polysaccharides of other types With the proteins of pneumococcus a delayed type of skin reaction was obtained The immediate wheal and erythema response was associated with the presence of type specific antibodies in the blood and with recovery from infection Cases which terminated fatally did not develop a positive skin test Two of the cases of Type I pneumonia developed positive wheal and erythema reactions although they had received no serum therapy Subsequently Francis and Tillett (28) noted the appearance of skin sensitivity to several types of pneumococcal polysaccharides in patients who had received repeated intracutaneous injections of 10 μg each of these other polysaccharides as controls for the specificity of the antibody response and found that these individuals had also developed circulating antibodies to these other pneumococcal polysaccharides Unlike the antibodies appearing in convalescence these heterologous antibodies appeared one to 3 weeks after recovery 10 of 18 patients formed heterologous antibodies and developed immediate skin sensitivity to the corresponding heterologous polysaccharide a group of 31 pneumonia patients who were not skin tested failed to develop heterologous antibodies during convalescence These findings were confirmed by Finland and Sutliff (29) Finally Francis (30) demonstrated that injection of 10 μg of purified Type I polysaccharide into normal humans resulted in the development of wheal and erythema skin sensitivity and of type specific agglutinins precipitins and protective antibodies in the serum A sample of Type I *pneumococcal polysaccharide which had been degraded* with alkali also showed *the capacity to produce immediate skin sensitivity*

and circulating Type I antibody It was also noted that tests for protective antibody were more sensitive than the skin test Numerous other studies by Felton and coworkers (31) have also shown correlations between antibody content and skin sensitivity following immunization With other types of
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ings led to extensive investigation of the use of the pneumococcal poly saccharide for immunization of man (cf 33 34) including a large scale field trial which showed their effectiveness in providing active type specific immunity against pneumococcal pneumonia (35) the existence of an antigen antibody system associated with wheal and erythema type sensitivity does not appear to have stimulated the interest of the allergist

There are many other aspects of the problem which are also intriguing In 1933 Francis (36) proposed the use of an intracutaneous skin test with polysaccharide as a guide to therapy In his original study in which horse anti pneumococcal serum was used in therapy he noted that the skin reac tion did not appear to depend upon the presence of this antibody but upon the host s reactivity which probably represents the active formation of antibody such as encountered in the untreated patients Finland and Sutliff (37) however using 5 ml of a Felton antibody concentrate from horse serum reported the ability to induce a wheal and erythema response passively in a normal subject which lasted for about 6 hours this would suggest passive transfer of the wheal and erythema response with concentrated horse antibody solutions Other Felton solutions failed to do this however It is of interest in this connection that while horse anti pneumococcal sera have always failed to produce passive anaphylaxis in the guinea pig Bailey and Raffel (38 39) reported obtaining passive anaphylaxis with Felton anti pneumococcal antibody solutions These discrepancies deserve clarification When rabbit anti pneumococcal sera came into use (40) it became evident that rabbit antibody could passively sensitize human skin so that the Francis [illegible]

guide to rabbit serum therapy and indicated the need for using highly purified polysaccharide preparations to avoid non specific reactions espe cially to the group specific C carbohydrate Wood (42) was able to obtain a positive wheal and erythema reaction in human skin on intracuta neous passive transfer of as little as one unit of rabbit anti pneumococcal serum to 5 normal subjects Passive transfer to a normal subject was also accomplished by giving serum from a pneumonia patient who had been treated with rabbit anti pneumococcal serum until the Francis test was positive In patients treated intravenously a positive wheal and erythema reaction to homologous polysaccharide was not obtained until a circulating antibody level of 0 1 unit or more per ml was reached Also worth mention ing is the finding that in 2 patients with Type VII pneumonia who received bivalent rabbit Type V and Type VII antiserum the skin test to Type V became positive after 50 000 units while 1 160 000 and 1 800 000 units of Type VII were needed indicating the magnitude of the *in vivo* antigen antibody reaction in serum therapy Wood (42) also noted that while

patients were critically ill the reactivity of the skin was greatly reduced Dingle and Seidman (43) using antiserum to *Hemophilus influenzae* type B noted a positive skin test in patients treated with rabbit antiserum but not with horse antiserum

With respect to passive transfer it is of interest to note that Finland and Sutliff (37) accomplished this with 130 ml Type II human convalescent anti pneumococcal serum in a patient who developed a positive wheal and erythema test within one hour The test could no longer be elicited a few days later

It is obvious that the system is ideal in many re pects for fundamental work in allergy in man using homologous and heterologous antibodies The antigens as well as the antibodies are readily obtainable in purified form and much data are available on their properties and immunochemical behaviour With the abandonment of serum therapy in the treatment of *pneumonia this problem was not pursued further*

History however has a strange way of repeating itself and with the introduction of the use of dextran as a plasma volume expander in man (44) it was noted that some humans receiving injections of certain dextrans developed allergic reactions of an anaphylactic type (45 46) with some dextrans the incidence was as high as 50 percent while with others the reac tions were much less common (47 48) Dextrans are bacterial polysac charides built up exclusively of glucose and it was at first thought that they were non antigenic (44) Prior to the studies reported above the pneumo coccal polysaccharides had also been thought to be non antigenic in man an over extrapolation from their non antigenicity in the rabbit

By analogy with the antigenicity of the pneumococcal polysaccharides in man (30 35) it was possible for us to demonstrate very simply that injection of 1 mg of dextran into humans resulted in the production of preci pitating antibodies to dextran and of wheal and erythema sensitivity (49) These findings were confirmed by Maurer (50) In large scale field trials in humans with dextrans which had the capacity to cause allergic reactions a high degree of correlation was found between the existence of wheal and erythema skin sensitivity before infusion and the development of an allergic reaction to dextran (51) Similarly correlations could be obtained between the presence of precipitating antibodies to dextran before infusion and the development of allergic reactions (51)

The incidence of skin reactions to dextran in populations not deliberately exposed to dextran was higher with dextrans with more complex branched structures than with straight chain dextrans It was also considerably higher with native dextrans than with the partially hydrolyzed dextrans used as plasma expanders These findings called attention to the need for using straight chain dextrans and for eliminating higher molecular weight materials from dextrans prior to their use as plasma expanders as had been done by one manufacturer who had produced a dextran with a low incidence of allergic reactions (51) Based on these findings, it was [illegible]

and of skin sensitivity to dextran in random populations Neill Sugg Hehre and Jaffe (52) have shown that dextran is a common contaminant of

naturally of interest to determine whether normal rats had precipitating antibodies to dextran which might account for this effect In some studies carried out in this laboratory (64) Mr Peter Z Allen found no evidence for such precipitins Neither could Halpern et al (62) find any evidence for the action of dextran attributable to a capacity to liberate anaphylatoxin *in vitro* from rat serum This negative evidence might suggest that dextran

saccharides and their relation to skin sensitivity Quantitative studies of the ability of human antibody to produce passive systemic and local anaphylaxis in animals as compared with anti polysaccharide produced in other species will also be of substantial importance

The dextran antidextran system consisting as it does of an antigen made up exclusively of a single sugar has proven invaluable in studies on the relation of immunological specificity and chemical structure (65) Its use has made it possible to obtain information about the size of the combining site on the antibody molecule and has revealed that antibodies are heterogeneous with respect to the extent of the complementary areas on their combining sites (65 66) How this heterogeneity may influence the skin sensitizing properties of these antibodies remains to be determined in the future

SUMMARY

Efforts to attribute the capacity of rabbit antisera to crystalline egg albumin and of human diphtheria antitoxic sera to sensitize human skin passively so that a wheal and erythema response occurs on contact with antigen will be examined critically Evidence will be presented to show that the sensitizing capacity of these sera is due primarily to the presence of antibody to antigens present as impurities in the preparations used for immunization The need to evaluate the extent of contamination of all antigens with impurities as a basic part of any investigation will be emphasized The capacity of the pneumococcal polysaccharides and dextran to immunize humans with the development of wheal nd erythema skin sensitivity will be considered and the advantages to tl of studying polysaccharide will be stressed

RÉSUMÉ

L auteur etu nere critique les tenta cte faites pour attribuer lapins anti-ovalbumi humain anti diphterique sensibiliser passiv humaine permettant d papulo-e l injec tion de l antigene des preuves q de sen sibilisation de ces essentiellem d un corps a l egard pour unisation

commercial sugar and these workers (53 54) have also isolated dextran producing organisms from the gastrointestinal tract so that ample opportunity exists for an antibody response It is also well established that dextrans cross react with Types II XII, XX IX XXII (55 56) horse and rabbit anti pneumococcal sera so that in some instances skin sensitizing antibody and the precipitins might possibly be a consequence of previous contact or infection with these organisms Maurer (50) however found that immunization of humans with dextran did not affect their Type II XII or XX anti polysaccharide levels nor did absorption with these types of pneumococcal polysaccharides reduce their antidextran levels

Recently Miss Bezer and I (57) have been able to obtain data on the relation of the molecular weight of dextran and its capacity to induce antibody formation and skin sensitivity in man Commercial Solvents Corporation had prepared for the National Research Council a series of fractions of partially hydrolyzed dextrans of the B512 strain which now is used almost exclusively as a plasma expander These fractions ranged in molecular weight from 16 400 to 412 000 and were subjected to careful fractionation to reduce the extent of polydispersity When these fractions were injected into human beings it was found that fractions of molecular weights 90 700 135 000 and 194 000 gave rise to precipitating antibodies in over 10 of 18 subjects an incidence not significantly different from that found with native dextrans in man However with fractions with average molecular weights of 51 300 35 000 and 10 600 only 1 of 29 individuals showed a significant antibody rise of 2 μg N per ml or more between the pre and post immunization serum samples Quantitative precipitin tests on the sera of these individuals using the native B512 dextran gave essentially similar results 12/17 who received the fractions with molecular weights of 90 000 or above showed a significant rise in antibody as compared with 1/29 who received the three fractions of lower molecular weight It is evident that with products of molecular weight 50 000 or less a significant decrease in the capacity to stimulate the formation of antidextran occurs

The findings in this study with respect to skin sensitivity are of interest With the dextran fractions the level of circulating antidextran which was associated with a definite wheal and erythema reaction was about 7 to 8 μg AbN/ml However in individuals immunized with native dextrans in the earlier studies and skin tested with native dextran positive wheal and erythema reactions were observed with as little as 2 to 3 μg AbN/ml (49) Evidently lowering of molecular weight reduces the capacity of dextran to elicit a skin reaction in immunized individuals This is completely consistent with the findings in the random populations studied in which a much higher proportion of individuals showed skin sensitivity to native dextran than to the clinical dextrans

As yet using the available antidextran sera with quantities of antibody N from 1 to 8 μg passive transfer in humans has not been accomplished The findings thus far would suggest that considerably larger amounts of human antidextran would be needed to sensitize skin passively than are required with rabbit anti pneumococcal antibody as seen from Wood s studies (42)

Also worthy of further attention is the problem of the action of dextran as a histamine liberator in certain species notably the rat (58 63) It was

naturally of interest to determine whether normal rats had precipitating antibodies to dextran which might account for this effect In some studies carried out in this laboratory (64) Mr Peter Z Allen found no evidence for such precipitins Neither could Halpern et al (62) find any evidence for the action of dextran attributable to a capacity to liberate anaphylatoxin *in vitro* from rat serum This negative evidence might suggest that dextran has a direct histamine liberating effect in the rat As such it is ae usful tool for studying histamine liberation and the factors influencing it (60 61)

Obviously much remains to be done in the study of antibodies to polysaccharides and their relation to skin sensitivity Quantitative studies of the ability of human antibody to produce passive systemic and local anaphylaxis in animals as compared with anti polysaccharide produced in other species will also be of substantial importance

The dextran antidextran system consisting as it does of an antigen made up exclusively of a single sugar has proven invaluable in studies on the relation of immunological specificity and chemical structure (65) Its use has made it possible to obtain information about the size of the combining site on the antibody molecule and has revealed that antibodies are heterogeneous with respect to the extent of the complementary areas on their combining sites (65 66) How this heterogeneity may influence the skin sensitizing properties of these antibodies remains to be determined in the future

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RÉSUMÉ

L auteur etudie d une maniere critique les tentatives qui ont ete faites pour attribuer au serum de lapins anti ovalbumine et au serum humain anti diphterique la propriete de sensibiliser passivement la peau humaine permettant d obtenir une reaction papulo érythemateuse a la suite de l injection de l antigene L auteur apporte des preuves que la propriété de sensibilisation de ces serums est due essentiellement a la presence d un anticorps a l égard des impuretes coutumes dans l antigene utilisé pour l immunisation

L'auteur insiste sur l'importance d'évaluer le degré de contamination des antigènes par des impuretés et de considérer cette donnée comme *fondamentale pour toutes les recherches dans ce domaine*

L'aptitude des polysaccharides pneumococciques et du dextran à sensibiliser l'homme avec l'apparition d'une réaction cutanée erythemato-papuleuse du type immédiat est étudiée et les avantages que les allergologues peuvent tirer de l'étude des substances polysaccharidiques sont soulignés

ZUSAMMENFASSUNG

Es werden kritisch alle Arbeiten untersucht mit denen man versuchte den gegen kristallisiertes Eialbumin gerichteten Kaninchen Antiseren und den menschlichen Diphtherie Antitoxinen die Faehigkeit zuzusprechen die menschliche Haut passiv so zu sensibilisieren dass bei Kontakt mit dem Antigen Urticaria und Erythemreaktionen ausgeloest werden

Es wird gezeigt dass die sensibilisierende Faehigkeit dieser Seren vorallem durch die Anwesenheit von Antikoerpern bedingt ist die gegen Antigene gerichtet sind die als Verunreinigungen in den fuer die Immunisierung verwendeten Praeparationen vorhanden sind

Es wird die Wichtigkeit betont den Grad der Verunreinigung aller Antigene abzuschaetzen und diese Angabe als Basis fuer alle in dieser Richtung hin anzustellenden Versuche zu verwenden

Die Faehigkeit von Pneumokokkenpolysacchariden und Dextran die Menschen mit nachfolgender Ausbildung einer urtikariellen und oetdematoesen Hautueberempfindlichkeit zu immunisieren, wird studiert und es werden *die Vorteile die im Studium des Polysaccharidsystems liegen* fuer die Allergieforscher herausgestrichen

RESUMEN

El autor examina criticamente los diversos trabajos en los que se trata de demostrar que el suero de conejo antiovalbumina y el suero humano antidifterico poseen propiedades sensibilizantes de la piel humana de tal manera que el contacto ulterior con el correspondiente antigeno produce una reaccion especifica Se demuestra que en realidad las propiedades sensibilizantes son debidas a anticuerpos contra ciertas impurezas presentes *en los antigenos usados para la immunizacion y se hace notar la necesidad* de determinar cuidadosamente estas impurezas en todas las investigaciones

El autor se refiere a la capacidad que presentan los polisacaridos de los neumococos y el dextran de inmunizar al hombre y producir la aparicion de sensibilidad cutanea y recalca la importancia y las ventajas de estos *sistemas en las investigaciones alergicas*

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PROPRIÉTÉS IMMUNO CHIMIQUES ET PHYSICO CHIMIQUES DES ANTICORPS PRÉCIPITANTS

par

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Dans la grande majorité des cas en Biologie la decouverte d un pheno mene précede de beaucoup l isolement et la caracterisation du compose qui en est responsable Il en a eté ainsi dans le cas des anticorps dont l existence a éte admise à partir du moment ou on a mis en evidence leurs activités leur isolement et la détermination de leurs propriétes physiques et chimiques n ont debute que bien plus tard Entre temps plusieurs activites des anti corps ont ete observees protection contre une infection par un agent patho gene neutralisation d une toxine agglutination de microbes ou de cellules précipitation specifique d un antigene en solution fixation du complément en présence de l antigene etc La diversite des effets provoques par les anticorps avait fait penser qu a chacun de ces effets correspondait un anti corps different d ou la notion qui a persiste longtemps de la multiplicité des anticorps et d ou les noms differents utilises pour les désigner aggluti nines precipitines lysines ambocepteurs antitoxines etc Cependant en opposition a cette hypothese de la multiplicite des anticorps ayant des activités differentes certains auteurs ont propose la notion de l unicite des anticorps en admettant que le meme anticorps peut se manifester par diverses activites Des resultats experimentaux sont venus etayer cette derniere hypo these Les plus nets et les plus classiques sont probablement ceux qui ont eté obtenus avec les anticorps anti polyosides pneumococciques il a ete prouvé que ce sont les memes anticorps qui agglutinent les pneumocoques encapsules qui provoquent le gonflement des capsules qui precipitent les polyosides purifiés lorsqu ils sont en solution qui facilitent la phagocytose des microbes et qui protegent un animal ou l homme contre l infection par un germe virulent a condition toutefois qu il s agisse bien du meme type de pneumocoque

Cependant des donnees precises obtenues surtout dans des recherches récentes nous obligent maintenant à admettre une heterogéneite des anti corps meme lorsqu ils sont formes envers un antigene pur et homogene C est sur cette heterogeneite des anticorps que nous allons insister dans ce rapport.

Il serait vain de tenter de décrire brièvement l'ensemble des connaissances actuelles sur les anticorps et nous nous excusons des nombreuses omissions que présente ce rapport (*) Mais nous avons préféré tout en passant en revue les principales propriétés des anticorps insister surtout sur trois aspects de la question a savoir 1° la définition des anticorps précipitants 2° l hétérogénéité de certaines de leurs propriétés physico chimiques et 3° l hétérogénéité de leurs spécificités

Le titre de ce rapport comporte le terme d anticorps « précipitants » tandis que celui du Professeur Kabat contient l expression d anticorps « allergiques » Or ces termes pourraient être interprétés différemment et amener des confusions

I En principe un *anticorps précipitant* est défini par le fait qu il forme un complexe insoluble en milieu physiologique lorsqu il se combine avec l antigène homologue dans des proportions convenables Cette définition présente des faiblesses et nécessite des commentaires

1 On admet *a priori* que l antigène est en solution ce qui n est pas obligatoire On peut aisément envisager des exemples d anticorps qui se fixeraient sur des antigènes qui ne sont pas en solution Or dans ces conditions comment peut on définir un « anticorps précipitant » ?

2 Dans la majorité des cas l antigène est une molécule volumineuse l anticorps l est toujours Ces molécules sont maintenues en solution par les relations étroites qui existent entre leurs groupements polaires et le solvant c est a dire l eau Lorsque le nombre des groupements polaires par rapport a la masse de la particule diminue la solubilité baisse L insolubilisation du complexe formé par l union d un anticorps avec l antigène homologue dépend donc en partie de la masse totale du complexe mais surtout du nombre de groupements qui restent libres et susceptibles de le maintenir en solution Ces groupements peuvent provenir soit de la molécule de l anticorps soit de celle de l antigène De ce fait la solubilité du complexe antigène anticorps peut dépendre de la solubilité initiale de chacun des composants et des proportions relatives de ces composants dans le complexe

L existence de complexes antigène anticorps solubles dans la zone d excès d antigène et dans le cas d anticorps anti protéine formés par le Cheval également dans la zone d excès d anticorps devrait pouvoir s expliquer par l importance relative de groupements restant libres et assurant ainsi la solubilité de ces complexes On sait d autre part que les anticorps anti protéines d un immunsérum de Cheval sont plus solubles que les anticorps anti polyosides du Cheval ainsi que les anticorps formés par exemple par le Lapin Notons enfin que différents systèmes antigène anticorps donnent des courbes de précipitation spécifique ayant des tracés qui diffèrent souvent entre eux par l extension du plateau du maximum de précipitation donc par la plus ou moins grande facilité de former des complexes solubles dans la zone d inhibition On peut ainsi aisément prévoir des cas où la formation de complexes antigène anticorps solubles serait facilitée parce que l antigène (ou le haptène) serait particulièrement soluble Il est probable qu une des raisons de la non précipitation des anticorps par des produits de dégradation

(*) Nous nous excusons aussi auprès des auteurs dont nous n avons pu citer les travaux

d'antigènes (*) est la formation de complexes solubles dont on admet l'existence puisqu'on observe une inhibition de la précipitation. On pourrait donc supposer que certains anticorps ne pourraient être mis en évidence à l'aide de la réaction de précipitation spécifique non pas parce que ces anticorps posséderaient des propriétés spéciales, mais parce que l'antigène en aurait

3. En plus des propriétés qualitatives que nous venons d'envisager, il ne faut pas perdre de vue l'aspect quantitatif de la réaction de précipitation spécifique. On peut admettre que la limite inférieure de visibilité d'un préci

ques. Ainsi, d'après nos estimations, la méthode d'hémagglutination passive des globules rouges tannés posséderait une sensibilité mille fois plus grande que la précipitation spécifique. Par conséquent, lorsque la quantité d'anticorps présente dans un sérum est très faible, et c'est le cas presque général, les sérums hyperimmunisés mis à part, il est parfois difficile de définir ces anticorps comme précipitants ou non précipitants tout simplement parce que leur taux est inférieur à la limite de la sensibilité de la méthode de précipitation spécifique.

4. Il n'est probablement pas inutile ici de mentionner que certaines espèces animales, comme le Chien, forment surtout des anticorps non précipitants, même lorsqu'on essaye de les hyperimmuniser. D'autres animaux, comme le Lapin ou le Cheval, peuvent former, à côté d'anticorps précipitants, des proportions variables d'anticorps co-précipitants (c'est-à-dire qu'ils sont entraînés dans l'ensemble d'une précipitation massive, mais ne forment pas de précipités par eux-mêmes) et d'anticorps non précipitants. La proportion de ces derniers peut être très grande. Ainsi Burtin a constaté, en utilisant un sérum de cheval hyperimmunisé avec de la sérum albumine humaine, qu'au moins 25 % de l'antigène se trouvait sous forme de complexes solubles même dans la zone d'équivalence. Enfin, on sait que le taux d'anticorps précipitants baisse souvent lorsqu'on conserve un sérum pendant des temps prolongés.

Ces quelques commentaires montrent jusqu'à quel point la tentative de définir une certaine catégorie d'anticorps par le fait qu'ils sont capables de former un précipité spécifique est fragile. Ils montrent aussi qu'il existe de nombreux cas où elle s'avère insuffisante ou même en défaut. Il semble donc qu'il faut être très prudent lorsqu'on veut classer des anticorps d'après ce critère et qu'il est souhaitable que d'autres critères soient adjoints lorsqu'on veut établir une classification.

II. D'une manière assez générale l'étude des *propriétés chimiques et physiques* des anticorps a été faite sur des produits isolés de sérums d'animaux hyperimmunisés. Or, comme nous allons le voir, quelques observations prouvent qu'il existe des variations de certaines propriétés des anticorps au cours de l'hyperimmunisation. Il n'est donc pas exclu que les anticorps qui apparaissent les premiers possèdent des propriétés qui les distinguent de ceux que nous allons passer en revue.

(*) On admet généralement que la principale raison de l'absence d'un précipité est l'impossibilité pour ces substances de participer à la formation d'un réseau (lattice).

Au cours de ces dernières années plusieurs mises au point sur les propriétés des anticorps ont été publiées et tout récemment une revue très complète et détaillée a été écrite par Isliker Pour ne pas dépasser les limites de ce rapport nous ne mentionnerons que les principales données

Tous les anticorps sériques connus possèdent les propriétés des globulines et il est impossible de les isoler du sérum a l état pur par des techniques chimiques ou physiques Les seuls procédés qui permettent de les extraire du serum a l etat pur sont basés sur leur combinaison spécifique avec l antigene On arrive dans certains cas à isoler des anticorps purs en partant de complexes antigène anticorps Dans la majorité des cas on est malheureusement obligé d employer des procédés assez drastiques (tels qu une forte acidité ou alcalinité l action d enzymes) et on risque d obtenir des produits partiellement modifiés ou même denaturés ou dégradés qui ne peuvent pas etre utilisés pour l étude des propriétés des anticorps initiaux Cependant l utili ation de résines synthétiques semble prometteuse

En partant de serums tres riches en anticorps on arrive a obtenir par des procedes physico chimiques des fractions de globuline composées surtout par des anticorps quelques unes des propriétés physiques des anticorps ont été déterminees sur de telles preparations

Les teneurs des anticorps en divers acides amines semblent etre identiques à celles des γ globulines d un sérum dit normal Ces dernières sont particulierement riches en acides amines cycliques (tyrosine et tryptophane) et peut etre en acides oxy aminés mais pauvres en acides glutamique et aspartique

On ne possede que peu de renseignements sur la structure intime des anticorps or pour comprendre la specificite de leur combinaison avec les antigenes il faudrait connaitre non seulement leur composition chimique globale mais aussi l enchainement et les positions respectives des acides amines dans la partie de la molécule d anticorps responsable de leur specificite Ce but n est pas facile a atteindre et de nombreuses recherches seraient nécessaires Parmi les moyens d y parvenir le plus sur serait de soumettre des anticorps a des clivages ménagés d isoler les fractions formees et d etudier leur comportement en face de l antigene homologue Si l on arrive a obtenir une sous fraction de masse moléculaire relativement faible et encore capable de réagir avec l antigene il serait possible d établir sa constitution précise comme on l a déjà fait pour certains polypeptides naturels et meme pour l insuline Le premier pas dans cette direction a éte franchi par Parfentjev lorsqu il a etabli sa methode de purification de l antitoxine de Cheval par digestion pepsique menagee on sait que la molecule originale est clivee mais que l activite antitoxique subsiste dans une des moitiés de cette molecule Plus récemment Porter a trouve que des produits de proteolyse partielle d un anticorps bien que depourvus de la capacité de precipiter l antigene peuvent provoquer une inhibition de la precipitation ils etaient donc encore capables de s unir avec l antigene Mais à notre connaissance une sous fraction active n a pas éte isolée et etudiee

Quelques determinations des groupements des anticorps participant à leur union avec l antigene ont ete tentees par des techniques de blocage de certaines fonctions definies Il semblerait que les groupements ε amines de la lysine et les acides amines cycliques jouent un certain role D apres Singer

le groupement specifique devrait comporter plus d un et moins de dix acides amines

Il existe actuellement plusieurs methodes qui permettent d identifier des groupements terminaux libres des protéines Quelques resultats de leur application a l etude des anticorps ont été publiés Ainsi Porter a trouvé que les anticorps de Lapin antiovalbumine possedent un seul groupement amine terminal et que l enchainement peptidique terminal de cet anticorps d ail leurs identique à celui des autres γ globulines du meme serum serait le sui vant alanyl leucyl valyl aspartyl (et probablement glutamyl) M^{me} Orlans a trouve egalement un groupement terminal d alanine dans l anticorps de Lapin anti sérum albumine bovine Cependant d autres auteurs en étudiant des anticorps bovins anti pneumocoque du type III ont observe plusieurs groupements terminaux Ce fait pourrait peut etre s expliquer par la plus grande masse moleculaire de ces derniers anticorps

L application des diverses méthodes d électrophorese a l etude des anti corps a permis de constater que dans la grande majorité des cas les anticorps precipitants font partie des γ globulines c est à dire que leurs mobilites electrophorétiques correspondent a celles qu on attribue a ce groupe de glo bulines Cependant on connait des cas ou des anticorps ont des mobilites plus grandes et si l on se conforme aux definitions originales des γ globulines d apres leurs mobilites on est amene à classer ces anticorps parmi les β glo bulines *Le cas le mieux étudie est celui des antitoxines ou plus généralement* des anti protéines formees par le Cheval Depuis de nombreuses annees on sait que les chevaux lorsqu on les immunise par des toxines ou anatoxines forment d abord des antitoxines qui ont des mobilités des γ globulines mais qu ensuite les antitoxines formees migrent plus vite On designe ces dernieres *soit comme fraction « T » soit comme* β_2 *ou* γ_1 *globulines Humphrey et* Porter ont observe un phenomene analogue chez des lapins les mobilites électrophoretiques des anticorps varient en fonction du temps d immunisa tion D apres Halliday les anticorps anti *Salmonella pullorum* chez les jeunes rats ont des mobilites des β globulines tandis que chez les rats adultes ils *migrent avec les γ globulines Les reagines syphilitiques auraient d apres* Laurell des mobilites differentes suivant le stade primaire secondaire ou tertiaire de la maladie en passant de la zone des γ globulines dans celle des β_2 globulines

Recemment Raynaud et Relyveld ont montre en fractionnant des serums anti *toxiques de chevaux* en determinant *la mobilite des fractions a l aide de* l immuno électrophorese et en etablissant des courbes de precipitation spe cifique que les antitoxines possedant la mobilite des β_2 globulines donnent des courbes de precipitation en cloche avec une pre zone tandis que les antitoxines lentes ayant la mobilite des γ globulines classiques donnent des courbes de precipitation du type Lapin c est a dire sans former des complexes solubles dans la zone d exces d anticorps

L existence d autres anticorps possedant des mobilites differentes de celles des γ globulines a ete signalee dans quelques autres cas tels que les anti corps anti tuberculine chez le Lapin et les anticorps formes par des poulets qui migreraient avec *les α globulines* Plusieurs etudes faites par differents auteurs des isohémagglutinines situent les mobilites de ces constituants dans une zone assez large des β globulines Or si l on se refere aux pro prietes antigeniques des iso hémagglutinines l utilisation des serums

ainsi que par A M Staub et leurs collaborateurs tandis que Morgan et Kabat avec leurs collaborateurs ont obtenu des resultats interessants sur les groupements specifiques des polyosides specifiques des groupes sanguins

En utilisant des sucres composes synthetiques et une réaction quantitative d inhibition de la precipitation specifique du dextran Kabat a conclu que le groupement determinant peut correspondre a une association de 6 sucres simples

Les faits deja connus ne nous permettent cependant pas de dire que tous les anticorps qui reagissent avec un antigene ou un haptene donne le font avec le meme groupement determinant de cet antigene ou avec toutes les parties d un groupement donne Nous savons au contraire que les anticorps meme ceux formes en réponse a l injection d un seul antigene homogene et pur presentent une heterogeneite de leur specificite

Nous revenons ainsi bien que sur un autre plan au probleme de l unicite ou de la pluralite des anticorps En effet si les anticorps envers un antigene donne sont heterogenes c est qu il y a pluralite des anticorps *Cependant il ne s agit plus maintenant de distinctions d apres les manifes*tations des anticorps mais d apres leur specificité c est a dire leur configuration chimique adaptee a la structure des groupements determinants de l antigene

Les preuves d une heterogeneite des anticorps diriges envers une seule substance ne manquent pas Deja Landsteiner et van der Schaer ont trouve qu en réponse a l injection d une proteine couplée avec deux groupements determinants différents l animal forme des anticorps dont une partie reagit avec l un des déterminants et une autre avec le deuxieme determinant Les nombreuses etudes faites sur des reactions croisees entre des antigenes de constitution chimique voisine et tout particulierement sur leur aspect quantitatif que nous devons a Heidelberger et a son ecole ont montré egalement qu une partie des anticorps seulement participe a ces reactions croisees On peut citer par exemple aussi le cas de la plaqualbumine que nous avons etudiée avec M[me] Kaminski La plaqualbumine se forme par un clivage enzymatique separant quelques acides amines de l ovalbumine la reaction de precipitation quantitative d un serum anti ovalbumine par cette derniere d une part et par la plaqualbumine d autre part permet de se rendre compte que le clivage des quelques 6 acides amines d une molécule ayant une masse moléculaire d environ 40 000 se traduit par une diminution de la quantite de precipite specifique une partie des anticorps anti ovalbumine ne reagit donc qu avec la molecule originale ou en d autres termes les acides aminés qui ont ete clives font partie du « motif antigenique » de la molecule de l ovalbumine Le terme de « motif antigenique » veut dire l ensemble des groupements qui sont responsables de la specificite immunochimique d un antigene

Deux possibilites peuvent etre envisagees en ce qui concerne la specificite globale d une molecule d antigene donc son motif antigenique » *a*) existence de differents groupements determinants situes dans des parties distinctes de la molécule les anticorps dans ce cas doivent posseder des configurations differentes et speciales pour chaque groupement *b*) le groupement determinant bien qu unique pourrait correspondre a une etendue qui varie occupant une surface plus ou moins grande de l antigene dans ce cas les anticorps doivent se differencier par leur adaptation a une

surface plus ou moins grande de l antigene mais tous devraient posseder une certaine specificite commune

Les resultats obtenus dans les etudes que nous avons mentionnees ne pouvaient pas fournir d arguments decisifs en faveur de l une ou de l autre de ces hypotheses qui d ailleurs ne s excluent pas puisqu on peut supposer egalement que le « motif antigenique » d une grosse molecule consiste en plusieurs groupements determinants presents dans des endroits distants de la molecule et que chaque groupement determinant est constitue par une association d un nombre plus ou moins grand de groupements chimiques

Quelques resultats recents permettent de discuter ces hypotheses Prenons le cas qui semblerait tres simple celui du dextran qui est constitue unique ment par des enchainements de glucose avec predominance de l enchaine ment α (1 6) De ses experiences d inhibition de la reaction de precipitation du dextran a l aide de divers composes plus simples Kabat a ete amene a envisager deux possibilites

1º que les zones structurales participant a la combinaison entre l antigene et l anticorps (« combining sites ») peuvent avoir des dimensions variables certaines correspondent a une chaine de 6 molecules simples d autres a un groupe de 4 ou 5 molecules ou bien 2º que les zones participant a la combi naison sont toutes de dimensions identiques mais que le degre d adaptation varie par rapport aux unites individuelles par exemple l adaptation pourrait etre tres stricte pour les trois chainons terminaux tandis que pour les autres le degre d adaptation pourrait varier

Le cas des antigenes proteiques est plus complique Mon collaborateur Claude Lapresle a pu montrer que les anticorps formes par le Lapin envers une proteine homogene et pure la serum albumine humaine sont en realite constitues par au moins trois anticorps ayant des specificites differentes En effet si la serum albumine est clivee a l aide d une protease endocellulaire on peut observer en utilisant en particulier l analyse immuno electropho retique que trois produits de proteolyse sont formes qui precipitent inde pendamment l un de l autre avec le serum de Lapin anti albumine Il s ensuit donc d une part qu il y a formation de trois anticorps differents contre la serum albumine et d autre part que la molecule d antigene ici la serum albumine humaine possede au moins trois groupements determinants differents situes dans des parties distinctes de la molecule

Plus recemment Raynaud et Relyveld ont repete des experiences du meme genre en utilisant la toxine diphterique Ils ont trouve que cet antigene possede cinq groupements determinants distincts et qu un serum « anti toxine pure » renferme au moins cinq anticorps differents qui reagissent tous avec la molecule entiere mais chacun avec une partie differente de la molecule D autre part ils ont constate que les anticorps formes par le Cheval a la suite de l injection de toxine sont au debut de l immunisation depourvus d action antitoxique vraie ils reagissent bien avec la toxine mais ne neutralisent pas le ou les groupements toxiques le precipite specifique reste toxique Par contre lorsqu on poursuit l immunisation les anticorps ont un pouvoir neutralisant reel ils reagissent avec le ou les groupements toxiques ces faits montrent donc aussi que des anticorps formes contre un seul et meme antigene peuvent reagir avec des groupements differents situes dans des parties differentes de la molecule d antigene

Des renseignements analogues peuvent etre tires aussi de nos etudes sur

les γ globulines humaines ainsi que des recherches effectuees sur les proteines de Bence Jones par nous meme en collaboration avec Burtin Fauvert et Hartmann et plus recemment par Scheidegger et Buzzi puis par Hassig Nous ne mentionnerons ici que quelques uns des resultats de ces etudes Certaines preparations de γ globulines purifiees industriellement soumises a l analyse immuno electrophoretique se sont revelees contenir deux constituants antigeniquement differents or ce fait ne pouvait etre constate qu avec certains immunserums ces serums contenaient donc des anticorps qui tous réagissaient avec des γ globulines normales mais pouvaient aussi distinguer deux sous fractions differentes ils possedaient ainsi au moins deux specificites differentes Les etudes sur les protéines de Bence Jones ont montre que l on peut les classer en plusieurs groupes d apres leurs reactions specifiques avec d s anticorps Tous les anticorps anti proteines de Bence Jones reagissent partiellement avec des γ globulines normales mais les anticorps anti γ globulines ne reagissent pas necessairement avec toutes les proteines de Bence Jones et généralement seulement avec certaines d entre elles En utilisant cinq immunserums equins anti serum humain normal de l Institut Pasteur et des sérums de lapin anti γ globulines Scheidegger arrive a la conclusion que la γ globuline humaine contient au moins cinq groupements determinants distincts et que ces groupements determinants se rencontrent dans l une ou l autre des proteines de Bence Jones differentes Les connaissances recemment acquises sur ces proteines permettent de les considerer comme des γ globulines incompletement synthetisees Elles seraient ainsi des parties ou fractions de la molecule naturelle normale de meme que dans les exemples cites plus haut les produits de proteolyse partielle *in vitro* d une proteine etaient des fractions de la molecule initiale mais dans le cas des proteines de Bence Jones il s agit de produits naturels bien que pathologiques

Les resultats de ces diverses etudes montrent que les anticorps formes en reponse a l injection d un seul antigene proteique pur et homogene sont multiples ils sont constitues par un melange en proportions variables de molécules dont la specificite peut correspondre a des groupements determinants situes dans des parties differentes de la molécule De plus comme nous l avons mentionne certaines experiences semblent justifier l idee que meme parmi les anticorps spécifiques pour un seul groupement determinant donné il y ait des molecules dont la specificite lui soit plus ou moins bien adaptee ou qui correspondent a des surfaces plus ou moins grandes de ce groupement determinant

Comme nous le disions au debut de ce rapport nous avons insiste surtout sur certaines proprietes des anticorps Nous croyons avoir montre que 1° La notion d anticorps precipitants n est pas un critere suffisant pour definir une categorie particuliere des anticorps et on connait des formes intermediaires entre les anticorps que l on classe facilement comme precipitants et ceux que l on appelle non precipitants Les anticorps se presentent donc comme heterogenes si on les envisage du point de vue de la propriete de former un precipite spécifique insoluble 2° L etude des proprietes physico chimiques des anticorps et particulierement de leurs mobilites electrophorétiques montre egalement une héterogeneite des anticorps puisque des anticorps specifiques pour un meme antigene peuvent chez le meme animal posseder des mobilites differentes

3° Les anticorps meme envers une substance antigenique pure et homo gene sont heterogenes du point de vue de leur spécificité L existence dans des immunserums de plusieurs anticorps en proportions variables et réagis sant avec des groupements determinants differents ou l absence dans certains immunsérums d anticorps spécifiques pour l un ou l autre de ces groupements determinants de l antigene presente des difficultés et meme des dangers d erreurs dans l interpretation de certaines constatations immu nochimiques elles obligent le chercheur a prendre des precautions

Dans l etat actuel de nos connaissances il n est pas possible de relier entre elles ces divers hétérogéneités mais on est tente d en chercher des explica tions valables Nous ne voudrions pas entrer ici dans la discussion du mécanisme de la formation d anticorps nous nous limiterons seulement a dire qu il est tres possible que le premier stade de ce mecanisme soit une dégradation partielle de l antigene les anticorps ne se formeraient donc pas contre toute la molecule d antigene mais contre des parties de cette molecule Ceci expliquerait facilement l heterogenéite de specificite et peut etre au moins partiellement l hetérogenéite dans la capacite de former des preci pites insolubles En effet des anticorps qui seraient specifiques pour les groupements determinants tres restreints ou n intervenant que peu dans la solubilite devraient donner des complexes solubles plus aisément que ceux qui bloquent justement des groupements dont depend la solubilité de l anti gene on pourrait faire le meme raisonnement au sujet des groupements des anticorps Mais il semble plus probable que l hétérogeneite dans les pro prietes precipitantes est due a la meme cause que l heterogeneite electropho retique Cette heterogeneite pourrait s expliquer en admettant que les anticorps synthetises dans des endroits differents de l organisme tout en possédant la meme caracteristique fondamentale de pouvoir se combiner avec l antigene presentent de legeres variations dues a leurs origines Nous savons par exemple que des differences dans les proprietes des anticorps s observent au cours de l hyperimmunisation c est a dire lorsqu on injecte des quantites croissantes d antigene ce qui doit amener l intervention d autres tissus que ceux qui participent initialement a l elaboration d anti corps De meme on observe des differences lorsqu on immunise un animal par diverses voies ce qui fait penser a la participation d organes diffe rents

Et pour conclure nous aimerions souligner que l heterogeneite des diverses proprietes des anticorps semble bien cadrer avec notre hypothese que leur formation fait partie d un mécanisme physiologique tres general de synthese des globulines adaptees a s unir plus ou moins spécifiquement a des sub stances définies ces substances pouvant etre aussi bien des produits du metabolisme que des produits de degradation cellulaire ou des substances exogenes Il nous semble qu il est plus aise de comprendre le role tantot utile tantot nefaste des anticorps ainsi que leur multiplicite et leur hetero geneite si on les envisage comme resultants d un mécanisme physiologique tres general

RÉSUMÉ

Au lieu de tenter de décrire en détail les nombreux renseignements que l on possède actuellement sur les anticorps l auteur a préféré tout en passant en revue leurs principales propriétés connues insister surtout sur trois aspects de la question la définition des anticorps dits « précipitants » l hétérogénéité de certaines de leurs propriétés physio chimiques et l hétérogénéité de leurs spécificités

La discussion de ces aspects l amène aux conclusions suivantes

1° La notion d anticorps « précipitants » n est pas un critère suffisant pour définir une classe particulière des anticorps La formation d un complexe insoluble n est pas un fait absolu il dépend de plusieurs facteurs de plus il existe des formes intermédiaires entre les anticorps franchement précipitants et ceux que l on appelle « non précipitants »

2° L étude des propriétés physico chimiques et particulièrement des mobilités électrophorétiques montre qu elles ne sont pas uniformes les anticorps sont physico chimiquement hétérogènes

3° Les anticorps même envers une substance antigénique pure et homogène sont hétérogènes du point de vue de leur spécificité ils réagissent avec des groupements déterminants différents situés dans des parties distinctes de la molécule d antigène

Il ne semble pas possible dans l état actuel de nos connaissances de relier d une façon bien définie ces diverses hétérogénéités entre elles mais l auteur tente de discuter les raisons de ces hétérogénéités et envisage la formation d anticorps comme un cas particulier d un mécanisme physiologique très général de synthèse de globulines adaptées à s unir d une façon plus ou moins spécifique à des substances définies ces dernières pouvant être aussi bien des produits du métabolisme que des produits de dégradation cellulaire ou des substances exogènes

SUMMARY

Instead of going into a detailed description of the numerous available informations on antibodies the author has chosen while he makes a survey of their main properties to insist particularly on three aspects of the matter the definition of so called precipitant antibodies the heterogeneity of some of their physico chemical pr[illegible] the heterogeneity of [illegible] specificities

The discussion of these [illegible] to the following c[illegible]

1° The concept of the p[illegible] body does not see[illegible] cient criterium to specify a[illegible] of antibodies

The formation of an insol[illegible] not an absolute [illegible] s on various [illegible] and bes[illegible] intermediate [illegible] characteri[illegible] cipitant [illegible] thers called [illegible] antibodie[illegible]

2° The [illegible] physic[illegible] es and s[illegible] electroph[illegible] n sho[illegible] l alike [illegible] bodies are [illegible] m the [illegible] t of

3° Even when produced by a pure and homogenous antigenic substance antibodies are heterogenous as their specificity is concerned they respond to different determinant groups located in distinct parts of the antigen molecule

In the present state of our knowledge it does not seem possible to link definitely together these various heterogeneities it is the author s aim to discuss the reasons He looks upon the formation of an antibody as on an individual case belonging to a very general mechanism of synthesis of globulines capable to combine in a more or less specific way with well defined substances

These substances may be metabolic products as well as products of cellular decay or of exogenous compounds

ZUSAMMENFASSUNG

Anstatt auf eine detaillierte Beschreibung der zahlreichen Arbeiten uber Antikorper einzugehen beschloss der Autor da er einen Ueberblick ihrer hauptsachlichen Eigenschaften geben soll auf drei Aspekte der Materie besonders grundlich einzugehen der Definition der sogenannten prazipitierenden Antikorper der Heterogenitat mancher ihrer physikalisch chemischen Eigenschaften und der Heterogenitat ihrer Spezifitat

Die Diskussion dieser Punkte erlaubt folgende Schlusse

1° Der Begriff dieser prazipitierenden Antikorper scheint kein genugendes Kriterium zu sein um damit eine eigene Art von Antikorpern zu definieren Die Bildung eines unloslichen Komplexes ist keine absolute Gegebenheit sie hangt von verschiedenen Faktoren ab und ausserdem gibt es zwichen den charakteristischen prazipitierenden Antikorpern und den anderen sogenannten nichtprazipitierenden Antikorpern Intermediarformen

2° Das Studium der physikalisch chemischen Eigenschaften und insbesonders ihres Verhaltens in der Elektrophorese zeigt dass sie nicht alle gleich sind und dass die Antikorper vom physikalisch chemischen Standpunkt aus heterogen sind

3° Bei Vorliegen einer renen und homogenen Antigensubstanz entsprechen die Antikorper da ihre Spezifitat heterogen ist verschiedenen determinierten Gruppen die an unterschiedlichen Stellen des Antigenmolekuls lokalisiert sind

Beim gegenwartigen Stand unserer Kenntnisse scheint es nicht moglich zu sein diese mannigfaltigen Heterogenitaten streng miteinnder in Verbindung zu bringen des Autors Ziel ist es aber ihre Ursachen zu diskutieren Er betrachtet die Bildung eines Antikorpers als einen besonderen Fall des sehr allgemeinen Mechanismus der Bildung von Globulinen passend fur ihre in einer mehr oder minder spezifischen Weise erfolgenden Verbindung zu genau abgegrenzten Substanzen Diese Substanzen konnten sowohl Stoffwechselprodukte Zellzerfallsprodukte als auch exogene Stoffe sein

RESUMEN

En lugar de hacer una descripción detallada de las numerosas propiedades actualmente conocidas de los anticuerpos el autor ha preferido insistir especialmente sobre tres aspectos la definición de los llamados anticuerpos «precipitantes» la heterogeneidad de algunas de sus propiedades físico químicas y la heterogeneidad de sus especificidades

La discusión de estos aspectos lo conduce a las siguientes conclusiones

1º La nocion de anticuerpo «precipitante» no es un criterio suficiente para definir una clase particular de anticuerpos La formacion de un complejo insoluble no es un hecho absoluto sino que depende de muchos factores Ademas existen formas intermedias entre los anticuerpos francamente precipitantes y los llamados «no precipitantes»

2º El estudio de las propiedades fisicoquímicas particularmente de las mobilidades electroforeticas muestra que los anticuerpos son fisicoquímicamente heterogeneos

3º Los anticuerpos aun aquellos provocados por una sustancia antigenica pura y homogenea son heterogeneos desde el punto de vista de su especificidad reaccionan con distintos grupos determinantes situados en diferentes partes de la molecula de antígeno

En el estado actual de conocimientos no parece posible vincular de una manera bien definida estas diversas heterogeneidades entre ellas pero el autor trata de discutir las razones de las mismas y considera la formacion de los anticuerpos como un caso particular de un mecanismo fisiologico general de síntesis de globulinas adaptadas a una union mas o menos específica con sustancias definidas Esta ultimas pueden ser tanto productos metabólicos como productos de degradación celular o sustancias exógenas

CELLULAR ANTIBODIES

by

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SUMMARY (*)

The concept that antibodies may persist in association with cells over a long period of time arose from several observations long persistence of the anaphylactic state in actively sensitized guinea pigs retention of anaphylactic reactivity in uterine horns of sensitized guinea pigs even after perfusion development of the concept of particular shock organs in man fixation of reagins in human skin and the phenomenon of localized or fixed eruptions Apart from the latter the corresponding antibodies usually were to be found in the serum at certain times

Similarly cell fixed antibodies were considered responsible for delayed hypersensitivities of the tuberculin type and for drug eruptions although a causal agent was not found in skin extracts or serum Support was provided when Rich and Lewis showed *in vitro* that tuberculin would damage cells explanted from tuberculin sensitive guinea pigs According to Cole and Favour failure to find a corresponding antibody in serum responsible for delayed type allergy can be explained by a masking

Direct evidence of a factor present in cells of individuals possessing tuberculin type and contact type hypersensitivities has been provided by the newer technique of cell transfer Disrupted cells (Lawrence) lead to transfer of delayed type r

months the transfer factor

The presence of transfer fac

component having the mobility of alpha globulin is reported to appear in cells of guinea pigs upon sensitization to chemical allergens (Jeter et al)

Indirect evidence pointing to cellular transfer (transfer by parabiosis and not by serum) requires careful appraisal

(*) The Editors express their regrets for not having been able to publish the full report, which the author failed to send them

A differentiation between the mechanisms that hinge upon classical antibody and cellular antibodies appears valid Both appear to represent separate but interrelated aspects of the immunological apparatus

RÉSUMÉ

La conception selon laquelle les anticorps peuvent rester pendant long temps associes a des cellules dérive de ces quelques observations la longue persistance de l etat d anaphylaxie chez le cobaye activement sensibilise le fait que la corne uterine du cobaye garde sa reactivite anaphylactique meme apres perfusion le developpement chez l homme d « organes de choc » la fixation des reagines dans la peau de l homme le phenomene des eruptions localisées ou « fixees » Il faut ajouter a ces observations la presence a certains moments dans le serum des anticorps correspondants

De meme les « anticorps fixes sur les cellules » ont ete consideres comme etant responsables de l hypersensibilité differee du type tuberculinique ainsi que des eruptions d origine medicamenteuse bien qu aucun facteur specifique n ait éte trouve ni dans les extraits de peau ni dans le serum Cette théorie a eté renforcee par les travaux *in vitro* de Rich et Lewis qui montreraient que la tuberculine endommage des cellules explantees provenant de cobayes sensibilises a la tuberculine

Selon Cole et Favour l impossibilité de trouver un « anticorps » correspondant dans le serum responsable de l allergie du type differe peut s expliquer par un effet « masquant » l anticorps etant mis en evidence par l isolement de proteines seriques en quantite appropriée (bien que la transfusion de serum complet reste inefficace dans les essais de transfert passif) mais il sera necessaire de fournir de nouvelles preuves a l appui de cette explication

On a pu obtenir par la méthode plus recente de transfert de cellules des preuves directes de la presence d une substance localisee dans les cellules de sujets presentant des hypersensibilites du type tuberculinique et du type « par contact »

Des cellules *desintegrees* (Lawrence) peuvent conférer une réactivite retardée à la tuberculine qui persiste pendant plusieurs mois on pense que le « facteur de transfert » est produit par les cellules filles nouvellement formees La presence dans le sérum du « facteur de transfert » n'a pas éte constatee

La presence d un nouveau composant ayant la mobilité de l alpha globuline a été signalee dans les cellules des cobayes après sensibilisation a des allergenes chimiques (Jeter et al)

Des preuves indirectes concernant le transfert cellulaire (transfert par parabiose et non par sérum) appellent une appreciation circonspecte

Une discrimination entre les mecanismes régissant les anticorps classiques et les « anticorps cellulaires » semble justifiee Tous deux semblent representer deux aspects différents mais relies entre eux de l appareil immunologique

ZUSAMMENFASSUNG

Die Auffassung dass Antikorper in Verbindung mit Zellen uber eine lange Zeitperiode persistieren konnen beruht auf verschiedenen Beobachtungen lange Dauer des Anaphylaxie Zustandes bei aktiv sensibilisierten Meerschweinchen Bestehenbleiben des anaphylaktischen Reaktionsvermogens in den Uterus Hornern von sensibilisierten Meerchweinchen auch nach Abtrennung Auftreten der Auffassung von hauptsachlichen Schock Organen beim Menschen Fixierung von Reaginen in der menschlichen Haut und das Phanomen der lokalisierten oder fixierten Eruptionen Abgesehen von letzteren werden die entsprechenden Antikorper gewohnlich zu gewissen Zeiten auch im Serum gefunden

In ahnlicher Weise werden zellfixierte Antikorper fur verzogerte (delayed) Ueberempfindlichkeiten des Tuberkulintypus und Medikamenteneruptionen verantwortlich gemacht obwohl kein kausales Agens in Hautextrakten oder im Serum gefunden werded konnte Unterstutzt diese Anschauung durch Rich und Lewis die *in vitro* zeigten dass das Tuberkulin von Tuberkulin empfindlichen Meerschweinchen herkommende Zellen schadigt In Uebereinstimmung mit Cole und Favour kann das Misslingen im Auffinden eines fur eine Allergie von verzogertem Typus verantwortlichen entsprechenden Antikorpers im Serum durch einen Maskierungseffekt erklart werden der Antikorper wird durch geeignete Isolierung der Serumproteine in hinreichender Menge dargestellt (obwohl Transfusionen des Gesamtserums sich in Versuchen eine passive Uebertragung zu erzeugen als wirkungslos erwiesen) weitere Beweise werden benotigt

Durch die neuere Technik der Zellubertragung konnte ein Faktor aufgezeigt werden der in den Zellen von Personen mit Ueberempfindlichkeiten vom Tuberkulin Typ und Kontakt Typ vorkommt Losgeloste Zellen (Lawrence) bedingen die Uebertragung eines verzogerten Reaktionsvermogens vom Tuberkulintyp der uber viele Monate persistierende Uebertragungsfaktor wird so nimmt man an auf die Tochterzellen ubertragen Eine Anwesenheit dieses Uebertragungsfaktors im Serum konnte nicht aufgezeigt werden Eine neue Komponente die die Beweglich von alpha Globulinen zeigt erscheint wie man berichtete in den Zellen von Meerschweinchen nach einer Sensibilisierung gegen chemische Allergene (Jeter et al)

Der auf Zelluebertragung fussende indirekte Beweiss (Uebertragung durch Parabiose und nicht durch das Serum) benotigt sorgfaltige Taxierung

Eine Unterscheidung zwischen Mechanismen die sich mit den Klassischen Antikorpern und den zellularen Antikorpern befassen scheint gultig zu sein Beide scheinen getrennte aber in Beziehung stehende Aspekte des immulogischen Apparates darzustellen

RESUMEN

El concepto de que los anticuerpos pueden permanecer fijados a las celulas durante largo tiempo se origina de varias observaciones persistencia del estado anafilactico en cobayos activamente sensibilizados reten

cion de la sensibilidad anafilactica por los cuernos uterinos de la cobaya sensibilizada aun despues de la perfusion la existencia de ciertos «órganos de choque» en el hombre la fijacion de las reaginas en la piel humana y el fenomeno de las erupciones localizadas o «fijas» Con la excepción del ultimo caso algunas veces se han encontrado los anticuerpos corespondientes en el suero

Asimismo los «anticuerpos fijados a las celulas» han sido considerados como los responsables del tipo «tardío» de sensibilidad tuberculinica o de las erupciones provocadas por drogas aunque el agente responsable no fuera encontrado en el suero o en los extractos de piel Un apoyo a esta hipótesis proviene del hecho demostrado por Rich y Lewis que la tuberculina lesiona *in vitro* las celulas de cobayos sensibles a la tuberculina De acuerdo con Cole y Favour el anticuerpo correspondiente no puede ser encontrado en el suero en los casos de sensibilidad de tipo tardío pues se encuentra «enmascarado» pudiendo ser aislado a partir de una cantidad adecuada de proteinas sericas (aunque la transfusión total del suero no puede producir la transferencia pasiva) estas ideas deben ser confirmadas

La tecnica reciente de transplante celular ha aportado pruebas directas de la presencia de una sustancia en las celulas de los indivíduos con sensibilidad de tipo tuberculínico o de contacto

La células «desintegradas» (Lawrence) pueden conferir una sensibilidad tardía a la tuberculina durable durante muchos meses por lo que se supone que el «factor de transferencia» no encontrado en el suero se trasmite a las celulas hijas

La presencia de un nuevo componente con la movilidad de las α globulinas ha sido señalada en las celulas de los cobayos sensibilizados por sustancias químicas (Jeter et al)

Las pruebas indirectas relativas a la transferencia celular (por parabiosis y no por suero) requieren una apreciacion cuidadosa

Una diferenciacion entre los mecanismos que vinculan los anticuerpos clásicos y los celulares parece justificada ambos representarian aspectos diferentes del sistema immunitario

ANTIBODY SYNTHESIS *

by

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This presentation will deal primarily with the metabolic and morphologic aspects of antibody synthesis during the response to serum protein antigens The use of this immunologic system as a model has several advantages First as seen in the human this antibody response is associated with a variety of typically allergic dermatologic vascular lymphoid and renal manifestations Second the immunologic and pathologic characteristics of this response in humans and experimental animals are quite comparable affording a satisfactory experimental situation for study And third the antibody formed can be readily isolated and quantitated and its synthesis studied by usual biochemical methods How generally applicable metabolic and morphologic data pertaining to this particular system will be to the field of allergic disease cannot be said It may be that one pattern of response will not apply to the synthesis of all reaginic cellular and precipitating antibodies

METABOLIC ASPECTS OF ANTIBODY SYNTHESIS

The timing of the metabolic processes in this antibody response has been worked out in some detail If a heterologous serum protein is injected into humans or experimental animals there is an initial or induction period of several days before the beginning of detectable antibody synthesis During the induction period the antigen equilibrates within the host s body fluids and is slowly catabolized Following the induction period as antibody begins to be formed it combines with the circulating antigen in the form of complexes which are usually rapidly eliminated from the circulation The rate of antibody synthesis increases rapidly until about

(*) This work was supported by Atomic Energy Commission Contract No AT (30 1) 1205

the time all circulating antigen is eliminated After the elimination of circulating antigen the rate of antibody synthesis falls rapidly Thus the entire response can be divided into an induction period a period of increasing antibody synthesis and a period of declining antibody synthesis

Little is known of the immunologic events transpiring during the induction period In the rabbit the length of this period varies from 4 5 days in the primary response to serum globulins to 7 9 days in the primary response to serum albumins and is 2 3 days in secondary responses to either kind of antigen In a series of excellent experiments Taliaferro and Talmage showed that little or no amino acid was incorporated into antibody or antibody precursors during the induction period (1) These experiments employed the transfer of lymphoid cells from secondarily stimulated donor rabbits to unstimulated recipients at varying intervals after injection of antigen By injecting S^{35} labelled amino acids into the donor prior to transfer of cells and isolating and determining the specific activity of the antibody formed by the transferred cells in the recipient the amount of labelled amino acid incorporated into antibody or antibody precursor during the induction period could be calculated These workers postulated that since there was little formation of antibody or antibody precursors during the induction period this period might be concerned with the production of antibody synthesizing enzymes Using a different approach the author and associates also found little incorporation of labelled amino acids into antibody or its precursors during the induction period (2)

The increase in the rate of antibody synthesis following the induction period is rapid and continues for several days until about the time antigen disappears from the circulation During this period amino acids are rapidly assembled into antibody molecules The time for this assembly

and observation of labelled antibody in the serum was only 40 minutes which means that in this time the amino acids reached the site of antibody synthesis were incorporated into antibody and the antibody was discharged into the blood (3) The precise rate of antibody synthesis during this period is difficult to determine since antibody as it is formed combines with antigen in the body fluids and cannot be measured directly However there is some evidence that the increase in rate during this period may be logarithmic (2)

Once the synthesis of antibody reaches its peak it then declines rapidly (2) In the primary response the rate of synthesis falls with a half life of a little more than one day below the levels of detectability (< 1 % maximum rates) within 15 days after injection of antigen Whether in the primary response the synthesis of antibody continues at a level below this could not be determined In secondary and hyperimmune responses however, there is in addition to an initial rapid fall in synthesis similar to that seen in the primary response a second period of decline In the secondary response once the rate of synthesis has fallen to 10 % of the maximum value the decline becomes slower In the hyperimmune response the second or slower rate of decline which has a half life of about 2 weeks begins once the rate of synthesis falls to about 20 % of the maximum Antibody synthesis is still considerable

1 month after injection and probably continues at detectable levels for several months

The significance of these rates of decline of antibody synthesis is not certain but they could reflect several things The initial rapid decline could parallel the loss of antigenic material or it could reflect the loss of a synthetic process such as an adaptive enzyme or inducer in the absence of antigenic stimulation or it could be dependent upon the loss of a short lived cell type involved in antibody production These alternatives are not mutually exclusive and their roles if any in the decline cannot be determined on the basis of available information The second slow phase of decline of antibody synthesis which increases in importance with repeated antigenic stimulation suggests a more lasting modification or adaptation of globulin synthesis It could reflect the rate of loss of a different more permanent cell type involved in the antibody response after repeated stimuli or the loss of an adapted globulin synthesizing mechanism

Intimately associated with the synthesis of antibody in this immunologic system is the combination of antibody with circulating antigen The serum protein antigens are unique in that in the absence of antibody they will persist in the circulation for long periods and are therefore present in considerable amounts when antibody appears Most other antigens are promptly eliminated from the circulation either via the kidneys (egg albumin) or by phagocytic cells (native non serum proteins chemically modified serum proteins polysaccharides and particulate antigens) It is this interaction of antibody with antigen in the circulation that appears to give rise to the characteristic disease serum sickness Recently it has been proposed that the antigen antibody complexes formed in the circulation during the phase of increasing antibody synthesis may themselves cause the disease (4 5) With labelled serum albumin antigens these circulating antigen antibody complexes can be easily demonstrated by precipitating the serum globulins with 50 % saturated ammonium sulfate and determining how much labelled antigen is bound to the globulin (6 7) In support of this proposed pathogenesis for serum sickness concentrations of antigen and probably antibody can be localized in developing lesions of arteries and kidneys using immunohistochemical techniques (5) Just how this antigen (presumably in the form of antigen antibody complexes) which is localized in the lesion may be involved in its pathogenesis remains to be determined However such complexes are capable of initiating anaphylactic and inflammatory reactions in experimental animals (8 9)

MORPHOLOGIC ASPECTS OF ANTIBODY SYNTHESIS

The sequence of morphologic developments that transpire during the synthesis of antibody to serum protein antigens can now be considered in relation to the progression of immunologic events just described In order to learn which cells are capable of antibody synthesis the structural changes in these cells during antibody synthesis and precisely how much antibody a given number of cells can produce this problem was studied by cell transfer techniques In these experiments cells from rabbits previously immu

nized to either bovine albumin or gamma globulin but no longer synthesizing significant amounts of antibody were transferred subcutaneously to recipient rabbits incapable of making an immune response These recipients were adult rabbits which had either received 400 r whole body x radiation 2 days earlier or had been made tolerant or unresponsive to the specific antigen by exposure at birth At the time of transfer the recipients also received an intravenous injection of I[131] labelled antigen The immune response was then followed by serial serum antigen and antibody determinations and *morphologic study of the transferred cells in the subcutaneous* sites throughout the course of the response

The first experiments were intended to determine the amount of antibody a given number of lymphoid cells could synthesize during a secondary response (10) Approximately ½ billion cells obtained by teasing donor lymph nodes of previously stimulated donors were suspended in PVP (*) and injected subcutaneously into the ventral abdominal wall of x radiated recipients Immediately after transfer of cells each recipient received intravenously approximately 2 mg I[131] labelled antigen The antibody response which followed was a typical secondary response in terms of speed magnitude and immunochemical behaviour of antibody indicating that the previously sensitized transferred cells were responsible The amount of free antibody in the circulation of the recipient approximately one week after transfer was equal to 1/3 the wet weight of the transferred cells The total antibody synthesized by the transferred cells during this period was no doubt several times the amount found in the circulation since a considerable amount of antibody combines with circulating antigen and is promptly catabolized and antibody is also lost by ordinary metabolic turnover (half life 5 days) Therefore it would appear that during the first week after transfer the total

ferred cells did not participate equally in the response one must conclude that some antibody producing cells are probably capable of synthesizing an amount of antibody equal to several times their own weight in the first

are probably involved in any immune response or immunologic disorder

Other experiments were conducted to determine *which type or types* of cells were capable of producing antibody after transfer (11) Three sources of cells from donor rabbits were used cells teased from mesenteric and popliteal lymph nodes cells taken from oil induced peritoneal exudates and cells teased from the thymus The cell types from these three sources are shown in Table I After transfer and antigenic stimulation the lymph node and peritoneal exudate cells made sizeable responses while thymic cells even in doses five times those of the other cell types made relatively small responses This suggests either that thymocytes although morphologically identical to lymphocytes, are immunologically quite distinct from

(*) PVP Macrose Schenley Laboratories Inc

them or that thymocytes while immunologically as capable as lymph node cells were not sufficiently stimulated by the intravenous preparatory injections of antigen into the donor to be set for a secondary response

The comparable responses which followed transfer of either peritoneal [illegible]) [illegible] s of lymph node lymphocytes (approximately twice the number of lymphocytes in the peritoneal cell transfers) it is unlikely that the lymphocytes which made up only 11 % of the peritoneal cells were responsible for a major part of the responses resulting from peritoneal cell transfers In a like manner the transfer of peritoneal macrophages equal in number to the macrophages present in the lymph node transfers was not followed by a detectable response Further there was no correlation between the amounts of antibody formed and the number of macrophages in the lymph node suspensions or the number of lymphocytes in the peritoneal exudate suspensions suggesting that minor cell types in each preparation were not of prime importance It seems more likely that the lymphocytes were responsible for antibody synthesis in the lymph node cell transfers and that the macrophages were responsible in the peritoneal cell transfers If this is the case it is interesting to find such similarity between the antibody responses in the two situations The time of initiation and duration of the response the amount of antibody formed the immunochemical behavior of antibody were essentially the same with both peritoneal and lymph node cell transfers

In order to correlate the morphologic aspects of antibody synthesis by these two dissimilar cell populations serial morphologic (12) and immunohistochemical (13) observations of these transferred cells during the antibody response were carried out Employing the same experimental situation as used for the antibody studies cells from the transfer sites were obtained by biopsy or autopsy at different times during the response Smears of the cells at time of transfer revealed a frequency of cell types comparable to that seen in Table I One day after transfer the lymph node cells were readily recognized as lymphocytes widely scattered in the edematous subcutaneous injection site At this time in the peritoneal cell transfer sites many large macrophages some still containing oil droplets were easily identifiable Three to four days after transfer the cell population in the injection sites had changed considerably In both the lymph node and peritoneal cell sites the most conspicuous cells now were transitional or preplasma cells replacing the lymphocytes and oil containing macrophages [illegible]

The location of these cells intermingled with some remaining lymphocytes or macrophages strongly suggested that they were formed by differentiation of the transferred lymphocytes or macrophages This development of preplasma cells was not accompanied by significant mitotic activity From the fifth through the ninth day after transfer of either lymph node or peritoneal cells a maturation of the preplasma cells took place By the eighth day the primitive forms so prominent at the third and fourth days were almost

completely replaced by typical mature plasma cells These cells contained eccentric nuclei with coarsely clumped chromatin and a considerable amount

cellular changes noted by others during the secondary antibody response (14 26) However in the intact rabbit it was the hematogenous stem cells which through multiplication and differentiation gave rise to the plasma cell series The present observations would seem to indicate that the ability to form antibody and to differentiate into plasma cells is not the property of any one type of cell It may be that the entities we recognize as lymphocytes macrophages and stem cells are really functional stages of the same cell and that any of these forms can under proper conditions respond to antigenic stimulation in characteristic metabolic and morphologic manner If this is the case the preplasma cell and plasma cell would be two more functional stages in this scheme of lymphoid cells Whether the lack of mitotic activity associated with the development of plasma cells from the transferred lymphocytes and macrophages which differs from the considerable mitotic activity seen in the intact rabbit is related to the initiating cell type or whether it is associated with the effects of the transplantation of cells cannot be determined However it would seem that mitoses are not an absolutely essential element in the secondary antibody response

Immunohistochemical study of the transferred cells with the fluorescent antibody technique has shown considerable amounts of specific antibody in the preplasma and plasma cells supporting the contention that they are indeed the source of the antibody response As early as two or three days after transfer some of the preplasma cells had small but definite concentrations of antibody in their cytoplasm As these cells progressed toward mature plasma cells during the next few days their cytoplasmic antibody concentration increased markedly Since the immunologic evidence indicated that the antibody was made by the previously sensitized transferred cells the finding of antibody in the plasma cells would seem to be strong evidence that they were derived from the transferred cells

These immunohistochemical observations correlate well with the previously described studies of antibody synthesis During the two day induction period in the secondary response there was little uptake of labelled amino acid into antibody little differentiation of the transferred cells and no histologic evidence of antibody in the transferred cells During the next three to four days the rate of amino acid incorporation into antibody increased rapidly to maximum values Many preplasma cells appeared to differentiate from the transferred lymphocytes and macrophages and specific antibody was detectable in increasing amounts in the cytoplasm of these preplasma cells From the sixth day of the secondary response on the rate of amino acid incorporation into antibody declined rapidly the number of preplasma cells decreased and they were replaced by typical mature plasma cells Specific antibody was heavily concentrated in these plasma cells

These observations would seem to indicate that a variety of lymphoid cell types can on antigenic stimulation give rise to preplasma cells which

are responsible for most of the antibody synthesis The antibody formed by these cells is probably rapidly discharged into the circulation thereby accounting for the relatively low concentration of detectable antibody in their cytoplasm As the preplasma cells differentiate into mature plasma cells the tempo of antibody synthesis appears to decline The mature plasma cell tends to concentrate antibody in its cytoplasm perhaps as a result of a decline in the rate of discharge of the antibody it forms into the circulation

TABLE I

Differential cell counts
(% based on counts of 1 000 cells)

	LYMPHOCYTES	MACROPHAGES	POLYS	PLASMA CELLS	OTHER
Lymph Node	90	8	0 5	1	0 5
Peritoneal Exudate	11	71	16	–	2
Thymus	92	4	1	3	–

Mac ophage n lud m nocytes hist ocytes m sothel l c ll and ret cul end the l al c lls

SUMMARY

This presentation deals primarily with the metabolic and morphologic aspects of antibody synthesis during the response to serum protein antigens The metabolic events transpiring during this response can be divided into an induction period a period of increasing antibody synthesis and a period of declining antibody synthesis Since as has been shown with isotope uptake experiments there is little formation of antibody or antibody precursors during the induction period it has been postulated that this period might be concerned with the production of antibody synthesizing enzymes Following the induction period the rate of antibody synthesis increases rapidly perhaps at a logarithmic rate until about the time that circulating antigen is eliminated from the blood After this the rate of antibody synthesis declines rapidly with a half life of a little more than one day Following the primary response the antibody synthesis declines beyond the level of detectability within approximately one week of the time of maximum antibody synthesis In the secondary and hyper immune responses there is an initial rapid rate of decline of antibody synthesis followed within a few days by a slower component with detectable antibody synthesis for several months

Intimately associated with the synthesis of antibody in this immunologic system is the combination of antibody with circulating antigen It is this interaction of antibody with antigen in the circulation that appears to

give rise to the characteristic disease serum sickness Recently it has been proposed that the antigen antibody complexes formed in the circula tion during the phase of increased antibody synthesis may themselves cause the disease

A series of cell transfer studies has been undertaken in order to observe the cell types involved in antibody synthesis Lymph node cells and oil induced peritoneal exudate cells from previously immunized donor rabbits have been transferred subcutaneously to x radiated recipient rabbits and the morphologic sequence of cell types in the transfer sites has been followed during the antibody response Both lymph node cells (90% lymphocytes) and peritoneal exudate cells (70% macrophage) are capable of antibody production after transfer to x radiated recipients Both types of cell transfers gave rise to numerous preplasma cells within two or three days after transfer and to typical mature plasma cells within a week of transfer Using the fluorescent antibody tracer technic it has been possible to demonstrate the specific antibody in the maturing and the mature plasma cells developing in the cell transfer sites These observations suggest that a variety of cells in the lymphoid macrophage series can on antigenic stimulation give rise to preplasma cells and plasma cells which are capable of antibody formation

RÉSUMÉ

Dans ce rapport l auteur etudie les aspects metaboliques et morphologiques de la synthese des anticorps en reponse a l introduction de proteines sériques antigeniques

Les phases metaboliques qui suivent la stimulation antigenique peuvent etre divisees en une periode d induction une periode de production croissante d anticorps et une periode de declin de la synthese

Par l etude de la consommation d un isotope il a ete demontre que la production d anticorps ou d un precurseur est tres faible pendant la periode d induction De ce fait on peut considerer que cette periode correspond a la phase de production des enzymes necessaires a la synthese des anti corps

Apres une periode d induction le taux des anticorps synthetises augmente rapidement peut etre suivant une progression logarithmique jusqu a l élimination complete de l antigene circulant Puis le taux des anticorps synthetises decline rapidement avec une demi vie d un peu plus d une journee

A la suite d une stimulation primaire la synthese des anticorps decroit au dessous d un niveau decevable environ une semaine a partir du début de la synthese maxima

Au cours de la stimulation secondaire ou de l hyper immunisation on observe une chute rapide de la synthese des anticorps suivie apres quelques jours par un rythme plus lent bien que la synthese des anticorps se poursuive pendant plusieurs mois

La combinaison de l anticorps avec l antigene circulant est intimement associee avec le processus de la synthese des anticorps dans ce processus immunologique C est l interaction de l antigene avec l anticorps dans la

circulation qui provoque les symptomes caractéristiques de la maladie sérique Plus récemment on a suggéré que c'est le complexe antigène anticorps formé dans la circulation durant la phase de la synthèse accrue d'anticorps qui est responsable directement de la maladie sérique

Une série de recherches a été realisée afin d'établir quelle est la variété cellulaire qui est impliquée dans la synthèse des anticorps A cet effet on a transféré par voie sous cutanée des cellules des ganglions lympha tiques ainsi que des cellules d exsudats peritoneaux (obtenus par l injec- tion d huile) d un lapin donneur préalablement immunisé a un lapin receveur antérieurement irradié par des rayons X Les modifications mor phologiques des cellules transplantées ont été suivies régulièrement à la suite de l injection de l antigène a l animal receveur c est a dire durant la période de synthèse des anticorps

Il a été constaté que les cellules lymphatiques (90 % de lymphocytes) aussi bien que les cellules de l exsudat péritonéal (70 % de macrophages) sont capables de produire des anticorps après transfert a un animal receveur irradié Les deux variétés de cellules donnent naissance deux ou trois jours après le transfert a de nombreux pré plasmocytes et après huit jours a des plasmocytes typiques adultes En utilisant la méthode des traceurs fluores cents il a été possible de démontrer la présence indiscutable d anticorps spécifiques dans les plasmocytes en période de croissance et dans les plas mocytes adultes qui apparaissent a l endroit de l injection des cellules trans férées Ces observations indiquent que les cellules de la variété lymphoide macrophage peut donner naissance après une stimulation antigénique a des preplasmocytes et a des plasmocytes normaux capables de synthe tiser des anticorps

ZUSAMMENFASSUNG

Diese Mitteilung behandelt vor allem die metabolischen und morpho logischen Aspekte des Aufbaus der Abwehrkörper welche als Reaktion auf die Einführung der antigenischen Serum proteinen entsteben

Die metabolischen Phänomene welche während dieser Reaktion auftreten können mehrere Stadien haben eine Vorbereitungsperiode eine Wach tumsperiode während der sich Antikörper bilden und eine Periode des progressiven Abnehmens

Da sich wie bei Versuchen mit einem Isotop festgestellt wurde keine oder nur wenige Antikörper bzw deren Bildung vorausgehende Produkte entwickeln darf man annehmen dass sich in dieser Zeitspanne Enzyme bilden die das Entstehen von Antikörpern hervorrufen

Nach diesem ersten Stadium bilden sich in steigendem Masse Anti körper vielleicht einer logarithmischen Progression entsprechend bis zu dem Augenblick wo das im Blut zirkulierende Antigen ausgeschieden wird

Daraufhin sinkt der Produktionssatz der Antikörper schnell ab und für die Dauer von etwas mehr als 24 Stunden vollzieht sich ihre Entwicklung nur halb so schnell

Nach dem ersten Reaktionseffekt sinkt die Bildung der Antikörper unterhalbt ihres Wahrnehmungsniveaus ab und zwar etwa eine Woche

nach dem starksten Entwicklungsmoment Im Falle von sekundaren Reaktionen und hyper immunisierten Subjekten sinkt der Bildungsspiegel der Antikorper rapide ab und diese Bedingungen bleiben wahrend mehrerer Monate bestehen

Bei dieser Art der Immunitatsuntersuchung ist die Bildung von Antikorpern engstens mit dem gleichzeitigen Vorhandensein von Antikorpern und Antigenen im Kreislauf verbunden Zweifellos kann man der wechselseitigen Wirkung der einen auf die anderen das Auftauchen der Charakteristica der Serenkrankheiten zuschreiben Man hat kurzlich eine Theorie vorgeschlagen nach der die Storungen die man as Serum Krankheit bezeichnet und erscheinen im gleichen Augenblick wo die Antikorperbildung anwachst im Blut bildenden Komplexen Antikorper Antigen zuzuschreiben waren

Eine Reihe von Versuchen uber den Zellentransport wurden unternommen um festzustellen welche Zellen an der Bildung von Antikorpern beteiligt sind

Lymphatische Ganglionzellen und Zellen von Peritonaal Exsudaten (mittels Ölbehandlung gewonnen) von vorher immunisierten Spender kaninchen wurden auf subcutanem Wege auf Empfanger Kaninchen ubertragen die mit Rontgenstrahlen behandelt waren Daraufhin wurden solange die Antikorper Reaktion anhielt die morphologischen Zellverande rungen in dem organischen Ubertragungsmilieu untersucht Die lymphatischen Ganglionzellen (90 % Lymplocyten) sowie die Zellen von Peritonaal Exsudaten (70 % Makrophagen) vermogen nach ihrer Ubertragung Antikorper bei mit Rontgenstrahlen behandelten Tieren zu produzieren

Diese Zellenubertragung hat, 3 Tage nach der Übertragung die Bilsung zahlreicher praplasmatischer Zellen verursacht und im Laufe der folgenden Woche die Bildung von reifen Plasmazellen hervorgerufen

Unter Anwendung der fluoroskopischen Methode bei der Suche nach den Antikorpern konnten wir den spezifischen sich bildenden Antikorper entdecken der das Entstehen von reifen Plasmazellen in dem organischen Milieu hervorruft in das Übertragungen stattfanden

Diese Beobachtungen lassen vermuten dass zahlreiche der Reihe der lymphoiden makrophagen zugehorigen Zellen das Entstehen von Plasmazelled und Praplasmazellen aus denen Antikorper entstehen konnen auszulosen vermogen wenn sie selbst durch ein Antigen den Anstoss hierzu erhalten

RESUMEN

El autor trata especialmente los aspectos metabólicos y morfológicos de la síntesis de anticuerpos durante la respuesta a los antígenos constituidos por seroglobulinas Se observan un periodo de inducción un periodo de gran produccion de anticuerpos y un período en que la producción declina Los experimentos llevados a cabo con isótopos radioactivos indican que durante el periodo de inducción prácticamente no hay formación de anticuerpos ni de sustancias precursoras de anticuerpos por lo cual se ha supuesto que ese período esta dedicado a la síntesis de las enzimas que intervienen en la formación de los anticuerpos A continuación hay

un periodo en que la síntesis de anticuerpos aumenta rápidamente talvez *logarítmicamente hasta un momento en que los anticuerpos circulantes* comienzan a ser eliminados de la sangre Luego la velocidad de formacion disminuye rápidamente con una vida media de un poco mas de un día En el transcurso de la respuesta a la primer inyección de antígeno la sintesis de anticuerpos disminuye hasta hacerse practicamente despreciable *aproximandemente una semana después de haber alcanzado su velocidad* máxima Durante la respuesta secundaria o la hiperinmunizacion hay una disminucion rapida de la velocidad de formacion de los anticuerpos seguida pocos días después por una fase en la cual la síntesis de anticuerpos es demostrable durante varios meses

Intimanente asociada con la síntesis de los anticuerpos está la combinación de los anticuerpos con el antígeno circulante Parece ser que es justamente esta combinación la que origina la enfermedad del suero y recientemente se ha sugerido que los responsables son los mismos complejos de antigeno y anticuerpo formados en la circulación

Para poder estudiar los tipos de celulas que intervienen en la síntesis de los anticuerpos se han realizado una serie de experimentos en los que se han transferido subcutáneamente a conejos irradiados con rayos X células de los ganglios linfáticos y del exudado peritoneal obtenidas de conejos inmunizados Se ha encontrado que tanto las celulas de los ganglios linfaticos (90 % de linfocitos) como las del exudado peritoneal (70 % de macrofagos) son capaces de producir anticuerpos luego de su trasplante En ambos casos se observan numerosas células preplasmaticas al cabo de dos o tres días y tipicas celulas maduras una semana despues Mediante la tecnica de anticuerpos marcados con fluoresceina ha sido posible demostrar la presencia de anticuerpos en las celulas formadas en los lugares de tras

de los anticuerpos

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BIOPHYSICAL AND IMMUNOCHEMICAL PROBLEMS IN ALLERGY (*)

by

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Our understanding of the interactions between antigens and precipitating antibodies at the molecular level has been greatly advanced over the last twenty five years by the application of precise physico chemical methods Immunochemistry may be considered to have come of age as a scientific discipline in its own rights around 1935 when Heidelberger and Kendall (1) developed the classical quantitative precipitin test and proposed a rational and chemically acceptable mechanism for antibody antigen reactions By an intelligent application of the mass law Heidelberger and co workers concluded that the precipitin reaction may be considered to be the resultant of a series of competing bimolecular reactions between polyvalent antigens and antibodies leading to the formation of polymeric aggregates These ideas have since been confirmed by others (2 3 4) and at present the weight of experimental evidence suggests that precipitating antibodies are diva lent (5 6) and that the commonly used antigens are polyvalent This is the basis of Pauling s framework or lattice theory (7)

Precipitating antibodies can be isolated relatively easily By electro phoresis most of these antibodies have been shown to be $\gamma 2$ globulins and by ultracentrifugation their sedimentation constants appear to be of the order of 6 5 Svedberg units corresponding to a molecular weight of about 160 000 A notable exception is however offered by horse antisera Horse antitoxins were shown to have a mobility intermediate between that of β and γ globulins (8) and antipneumococcal antibodies were shown to have a sedimentation constant of about 18 S corresponding to a molecular

( ) Supported by grants from the Department of Health and Welfare Canada and the Institute of Allergy and Infectious Diseases National Institutes of Health Bethesda Md We are also indebted to the Charles E Frosst Co Montreal for financial assistance

weight of about 1 000 000 (9)(*) In comparison the understanding of the interactions—both *in vitro* and *in vivo*—between allergens and the corresponding antibodies produced in man is still rather vague (10 15) One of the main and obvious difficulties is that both skin sensitizing and blocking antibodies found in sera of allergic individuals do not give precipitates with allergens and thus cannot be readily isolated in a pure state for further physico chemical studies Another difficulty is that most of the common allergens are complex mixtures (e g pollens grasses, dusts danders foods) and are either non antigenic in experimental animals or else elicit, in other species but man the production of precipitating antibodies devoid of skin sensitizing ability (*)

The non precipitability of skin sensitizing and blocking antibodies has been attributed (17 18) to the possibility that both of these antibodies are univalent and therefore sufficiently large insoluble aggregates would not be produced even if firm combination between these antibodies and the

one would require the answers to both these possibilities a concerted research programme was undertaken in this laboratory to study both these aspects In view of the wide incidence of allergy (hay fever and asthma) to ragweed pollen on the American continent our main efforts over the past four years have been directed towards (a) the revelation of the chemical composition of the allergen(s) in ragweed pollen and (b) the elucidation of the nature of antibodies found in sera of ragweed sensitive individuals

The results of our studies on ragweed pollen will be presented at another

our purest

the allergenic

is a relatively

low molecular weight material (sedimentation constant = 1 20S composed of lysine arginine hydroxyproline glycine valine alanine norleucine and glutamic acid) and is capable of eliciting a positive skin test in amounts as little as 10 ^{7} mg Our results would also suggest that it is a polyvalent antigen

The present paper deals primarily with our attempts (*) to isolate and characterize the antibodies present in allergic sera by both physico chemical and immunochemical methods and the results are compared with related findings of other workers

(*) The diversity of precipitating antibodies has been discussed in great detail in a number of review articles (11 12 13 14 42)

(*) Note however, the findings of Sherman (16) with anti ovalbumin rabbit serum.

(*) Most of the results presented here have been obtained by MM J Gordon and L Gyenes and will be submitted in partial fulfillment for their Ph D degrees to the Department of Biochemistry McGill University

I PHYSICO CHEMICAL STUDIES

a) Electrophoresis

The results of our preliminary study published in 1955 (20) demonstrated that skin sensitizing activity to ragweed in seven allergic sera separated into electrophoretically distinct serum fractions by starch electrophoresis was found in the β and γ globulin regions A more detailed study and the use of a more refined technique (21) revealed that in fourteen sera skin sensitizing activity was associated with γ globulins with a tendency to reside primarily in the γ_1 globulin region The mobilities and purity of the serum fractions were determined painstakingly in a Tiselius electro phoresis apparatus In a few instances traces of activity were also detected in the β globulin region and were attributed to contamination by γ_1 globu lins This interpretation seems reasonable especially if one considers that γ globulins are electrophoretically heterogeneous and tend to be carried over the whole electrophoretic pattern into the region of α_1 globulins as disclosed by immuno electrophoresis (22 23)

A typical distribution of both the protein and skin sensitizing activity after electrophoretic separation is illustrated in Fig 1 The skin sensitizing activity of each eluate was estimated by comparison with reactions obtained in terms of tenfold serial dilutions of the original serum It is worthy of note that in at least two experiments maximum skin sensitizing activity was associated with fractions containing the smallest amount of protein (0 08 % protein or less) and in consequence one must conclude that (a) there is no correlation between this activity and the protein content of the fractions and (b) that the factor (s) responsible for skin sensitization must be in exceedingly low concentration and must possess a high biological potency

The possibility that the mobilities of the various isolated serum fractions may have been altered by interaction with the starch was fully realized and tested However no evidence was obtained to support this view None theless it was clearly stated (21) that the designation of the fraction located on the starch block between the slow gamma γ_2 and β globulins as γ_1 globulins and not as β_2 globulins might appear as somewhat arbitrary particularly since there are no objective and universally accepted criteria for the designation of the intermediate components located between the well defined β and slow γ globulin peaks

The results of other investigators (published until 1955) who have attemp ted to localize skin sensitizing antibodies by various methods were reviewed in these two papers (20 21) Of particular interest are the studies of Cann and Loveless (24 25) who have used one of the more refined electrophoretic techniques, namely electrophoresis convection A critical analysis of their results reveals however that their method did not permit complete separation of the various serum components and that activity was spread over fractions containing both β and γ globulins Nevertheless they concluded that their data supported the hypothesis that β globulins were chiefly responsible for reaginic activity but that the possibility of partici

pation by γ-1 globulins could not be excluded One may, therefore quite fairly conclude that the results of Cann and Loveless do agree in essence with the results obtained by starch electrophoresis in this laboratory

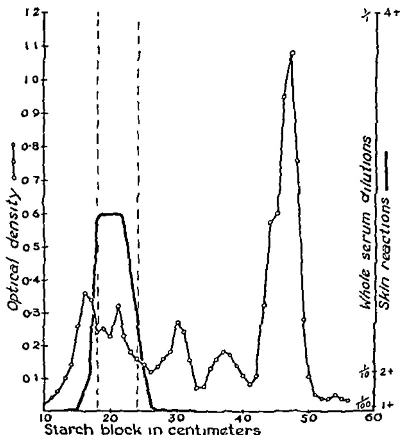


FIG 1 — Separation of allergic serum by starch electrophoresis The curve in heavy print represents distribution of reaginic activity estimated in terms of ten fold serial dilutions of the corresponding whole serum

and that the main difference is not one of interpretation but of nomenclature To support our results one may quote the more recent results of Brattsten et al (26) and of Humphrey and Porter (27) Brattsten et al have shown that skin sensitizing activity resided in the γ_1 globulin region when an allergic serum was separated by continuous electrophoresis on a starch block and Humphrey and Porter found that reaginic activity was also associated with a fast γ globulin fraction which has been isolated by chromatography on a cellulose ion exchange column It is indeed gratifying to find agreement amongst all these findings However it is interesting to note that in their last paper Cann and Loveless (28) reopened the argument about nomenclature and concluded that reaginic activity migrates electrophoretically with the β globulins It is surprising that they have overlooked the work of Brattsten et al (26) and that of Humphrey and Porter (27)

Fotunately with regard to blocking antibody there appears to be full agreement amongst different workers (29 30 31) that this factor migrates in an electric field as a slow γ globulin

b) Ultracentrifugal analysis

The paper by Sehon et al (21) appears to be the only one in which sedimentation characteristics of serum fractions containing skin sensitizing activity are reported Both γ_1 and γ_2 globulin fractions of allergic sera separated by starch electrophoresis were resolved in the ultracentrifuge into two components The sedimentation constant of the major component was 6 6 Svedberg units and that for the minor component was 18 20 Svedberg units Components with similar sedimentation constants are also found in the γ globulin fraction of normal sera (21 32)

More recently in this laboratory (33) whole sera of treated and non treated allergic individuals and of normal volunteers immunized with ragweed pollen were separated by ultracentrifugation (at 59 780 R P M) in partition cells similar to those described by Tiselius Pedersen and Svedberg (34) and by Yphantis and Waugh (35) Our results indicate that skin sensitizing antibodies are associated with the fast sedimenting serum components (sedimentation constant > 16 5S) and that blocking antibodies sediment as normal γ globulins (i e with sedimentation constant of about 6 5S)

II IMMUNOCHEMICAL STUDIES

a) The nature of skin sensitizing and blocking antibodies

The most striking feature of the skin sensitizing antibody is that it has the ability to sensitize normal skin and remains attached to the site of injection for prolonged periods (21 36) Its ability to sensitize skin is however lost on heating at 56 °C for periods of 1 4 hours (31 37) As far as this author is aware no unequivocal and direct evidence has been presented that skin sensitizing antibodies can combine in vitro with appropriate allergens Results obtained in this laboratory (38 39 40) which will be discussed later indicate that a firm combination does occur between the reaginic factor and the allergen On the other hand blocking antibodies have been suspected for a long time to be able to combine with the allergen (s) in vitro on account of their ability to inactivate the latter (31 36)

γ globulin serum Although the similarity between blocking antibodies and normal globulins was not explicitly brought out by these workers this conclusion is obviously implied in their results Thus blocking antibody would appear to possess at least antigenically similar properties to those of normal human globulins and to be capable of combining in vitro with ragweed components

b) In vitro detection of antibodies in allergic sera

In this section evidence is presented to show that in all probability both skin sensitizing and blocking antibodies to ragweed are divalent species and that the main reason for their having evaded detection by classical in vitro methods is their being present in exceedingly low concentration in

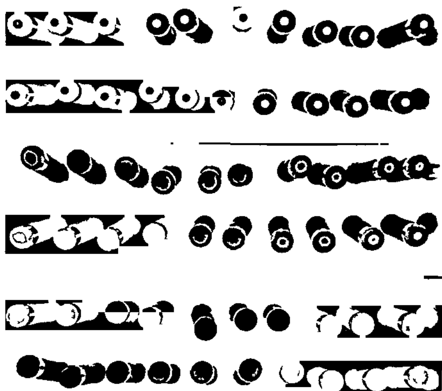


FIG 2 — Hemagglutination patterns
Each row represents tubes containing serum in halving dilutions the concentration of serum decreasing from left to right The top two rows represent a control experiment in duplicate with normal human serum no hemagglutination is observed in any tube The center two rows represent an experiment in duplicate with allergic serum *the patterns represent a gradual decrease in the extent of hemagglutination* The bottom two rows (in duplicate) represent hemagglutination patterns obtained with rabbit antiragweed serum The patterns in all 10 tub s are positive the actual titer of this serum was 10^7

allergic serum With this assumption in mind we have developed a specific and highly sensitive method which leads to the detection of these antibodies by the formation of easily visible aggregates in vitro (38 39) In essence this test is an adaptation of the methods described by Pressman Campbell and Pauling (56) and by Stavitsky and Arquilla (57)

For this purpose the *allergen is coupled to rabbit red cells by chemically* stable azo bonds bis diazotized benzidine being the coupling agent The

sensitized red cells are then suspended in the allergic serum If skin sensitizing and/or blocking antibodies are present specific gelatinous aggregates as shown in Fig 2, are produced In absence of antibodies the sensitized erythrocytes sediment to the bottom of the test tube to form a compact button, which represents a negative pattern This hemagglutination test is simple to perform the main problem being the choice of the correct ratio of bis diazotized benzidine to antigen for a given amount of red cells However once this is established no further difficulties are encountered and reproducible results are obtained in successive experiments The details of the method are described elsewhere (39)

The sensitivity of the method was established by evaluating it in terms of rabbit antisera containing precipitating antibodies to water soluble ragweed pollen extract (WSR)(*), bovine serum albumin (BSA) human serum albumin (HSA) and human gamma globulin (HGG) Positive ring tests were obtained with these sera in dilutions only as high as 1 64 whereas hema

TABLE I

Hemagglutination and inhibition experiments

ANTIGEN COUPLED TO RED CELLS	INHIBITOR	ANTISERUM	TITER (r c proc l of d lut on)
WSR	none	anti WSR #1+	10 000 000
WSR	none	anti WSR #5	250 000
WSR	WSR	anti WSR #5	8
WSR	none	anti BSA	no reaction
BSA	none	anti BSA	20 000
BSA	BSA	anti BSA	no reaction
BSA	WSR	anti BSA	20 000
HSA	none	anti HSA	40 000
HGG	*none*	*anti HGG*	*320 000*
HGG	HGG	anti HGG	no reaction
WSR	none	B P *	1 024
WSR	WSR	B P	no reaction
WSR	grass pollen	B P	1 024
WSR	wormwood pollen	B P	1 024

All ant a were produced in rabb ts Th serum des gnated B P was obta ned from a ragweed sens tiv ind du l

+ R peat d intravenous nject ons f lum p ecipitated WSR o er a per od of 2 — 4 *m nths we used for immun zat on Th oth r ant gens dissolved n sal ne wer* inj ct d intra en u ly

(*) Prepared accord ng to method described elsewhere (58)

(*) Expressed as reciprocal of the highest dilution still giving a positive reaction Usually the samples were evaluated in terms of two fold serial dilutions of the whole serum.

of free soluble antigen Thus addition of a solution of ragweed antigens to a system containing BSA sensitized erythrocytes and anti BSA serum had no effect on the extent of hemagglutination whereas addition of BSA completely inhibited the test Conversely addition of a solution of WSR to a system containing WSR sensitized erythrocytes and rabbit anti WSR serum or serum from a ragweed sensitive individual resulted in complete inhibition On the other hand addition of BSA or pollen extracts of other plants to this system did not interfere in any way with the test Reproducible results were obtained for any duplicate experiments done with the same serum and the same batch of sensitized erythrocytes, as illustrated in Fig 2 However using different batches of sensitized erythrocytes the titers varied within a factor of 16 i e $\pm$ 2 tubes

The specificity of this method is also borne out by the fact that ragweed coated red cells were agglutinated by each of the forty sera obtained from a group of thirty five non treated and treated ragweed sensitive individuals and by the three sera collected from normal subjects who received a series of ragweed injections No serum obtained from any ragweed sensitive individual failed to give a positive hemagglutination reaction On the other hand the hemagglutination test was negative when applied with ragweed sensitized erythrocytes to normal sera (20 sera) or to sera from individuals allergic to grass or aspirin All these results are listed in Table II, together with the hemagglutination and skin sensitizing titers As can be seen there exists some parallelism between hemagglutination and skin sensitizing titers This may be interpreted in terms of either of the following hypotheses (1°) that the hemagglutination and skin sensitizing abilities might be due to two distinct properties of one and the same molecule or (2°) that they are two independent factors formed concomitantly by non treated allergic individuals Furthermore it would appear that higher hemagglutination titers are given by sera of treated allergic individuals Since formation of blocking antibodies are induced on treatment and hemagglutination titers also increase on treatment one may suggest (1°) that the hemagglutination

TABLE II

Hemagglutination and Prausnitz Kustner tests *

NO OF SERUM	DONOR	HEMAGGLUTINATION TITER *	P K TITER
1 22	normal	no reaction	no reaction
SERA FROM INDIVIDUALS SENSITIVE TO OTHER ALLERGENS			
23	sensitive to aspirin	no reaction	no reaction
24	sensitive to grass	no reaction	no reaction
25	sensitive to grass	no reaction	no reaction

SERA FROM RAGWEED-SENSITIVE INDIVIDUALS •

26	non treated	64	10
27	non treated	128	100
28	non treated	64	500
29	non treated	128	100
30	non treated	256	100
31	non treated	1024	1000
32	non treated	16	positive+
33	non treated	32	positive+
34	non treated	256	not tested
35	non treated	64	(*)
36	non treated	64	100
37a++	non treated	4	(*)
37b++	treated	128	10
38a++	non treated	32	10
38b++	treated	128	(*)
39a++	non treated	512	250
39b++	treated	1024	250
40a++	non treated	128	not tested
40b++	treated	512	not tested
41a++	non treated	128	250
41b++	treated	2048	500
42	treated	256	1000
43	treated	512	1000
44	treated	32	10
45	treated	128	1000
46	treated	64	100
47	treated	128	500
48	treated	256	100
49	treated	256	100
50	treated	512	100
51	treated	32	(*)
5~	treated	16	(*)
53	treated	8	(*)
54	treated	128	500
55	treated	16	100
56	treated	64	100
57	treated	32	100
58	treated	32	100
59	treated	1024	1000
60	treated	2048	1000
61	treated	1024	positive+
62	treated	512	positive+
63	treated	128	not tested
64	treated	1024	not tested
65	treated	1024	not tested
66	treated	512	500

• ... e rea tion In of the whole

( ) The P K t t w s negat ve f r a t n f ld dilut n of the s rum The und luted s rum was not tested

++ Sera obtain d f m the same indi dual before treatm nt are r ferred to by letter ( ) and after treatment by l tt r (*b*)

factor is identical with blocking antibody (and that some blocking antibodies are produced even by non treated individuals in concentrations which are lower than those required for their detection by the standard in vivo test) or (2°) that blocking antibodies produced during desensitization are able to agglutinate sensitized red cells just as other factor(s) found in sera of non treated individuals

c) Further characterization of antibodies in allergic sera

To test the above hypotheses and in an attempt to clarify the nature of the hemagglutination factor(s) the following experiments were performed

The skin sensitizing activity of allergic sera of non treated individuals was destroyed by heating at 56 °C—for periods as long as 11 hours—without affecting the hemagglutination titers Similarly heating sera of treated allergic individuals or normal immunized subjects did not affect the hemagglutination titers Thus the hemagglutination factor(s) appeared to be thermostable

Sera of treated and non treated allergic patients were absorbed out with an equal volume of packed sensitized erythrocytes In each case the supernatants were shown to have been completely depleted of skin sensitizing and blocking antibodies and of any hemagglutination factor(s) This therefore demonstrates that firm combination had occurred between each of these factors and the ragweed pollen constituents coupled to the erythrocytes To prove that absorption of these factors was an immunologically specific reaction a serum from an individual allergic to both ragweed and grass pollens was absorbed out with ragweed sensitized erythrocytes The supernatant was shown to have been depleted of skin sensitizing and hemagglutination factors with respect to ragweed, but to have retained its skin sensitizing ability to grass pollen

At this juncture it is appropriate to present other evidence supporting our view that skin sensitizing and blocking antibodies as well as the hemagglutination factor(s) combine with ragweed pollen *in vitro* Water soluble ragweed antigens were coupled by covalent azo bonds to polydiazotized polyamino polystyrene (40) the resultant antigen polystyrene conjugate being an insoluble polymer The reactions involved in the preparation of this conjugate are shown in the flowsheet presented in Fig 3 Allergic sera were then exposed to this antigenic adsorbent and it was found that skin sensitizing and blocking antibodies together with hemagglutination factor(s) were completely and specifically removed Heterologous antigens coupled to polystyrene had no absorbing capacity for any of these factors found in sera of ragweed sensitive individuals This method was deemed to provide also the possibility of isolating these factors in a pure and concentrated form subsequent to their absorption by dissociating them from the ragweed polystyrene conjugate Although dissociation of ordinary precipitating antibodies can be readily effected (43) no satisfactory method has so far been devised for recovering the factors present in allergic sera

Next we turned to a number of fractionation procedures in the hope that these various factors could be separated from each other As mentioned earlier skin sensitizing and blocking antibodies were shown to migrate

electrophoresis (Spinco C P Apparatus) Hemagglutination ability was found to be associated with all serum sub fractions throughout the γ_1 and γ_2 globulin region, with which skin sensitizing ability was also associated

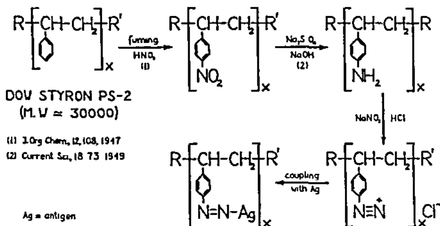
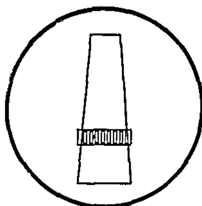


FIG 3 — Flowsheet of the preparation of polystyrene antigen conjugates

Similarly applying the chromatographic fractionation procedure on cellulose as used by Humphrey and Porter (27) it was shown that skin sensitizing antibodies and the hemagglutination principle(s) were always associated with each other Thus both zone electrophoresis and chromatography failed to divorce these factors from each other

Allergic sera on prolonged dialysis in standard Visking tubing did not lose their skin sensitizing and hemagglutination ability and these factors were not separated by ultrafiltration from the rest of the serum proteins It was therefore supposed that these factors were associated with serum components of a molecular weight higher than about 30 000 Finally fractionation of the factors in question was attempted in the ultracentrifuge (Spinco Model E Apparatus) in preparative cells provided with both fixed (34) and moving (35) partitions These cells are represented schematically in Fig 4 The results obtained with both cells were essentially identical but we feel that the cell of Yphantis and Waugh is to be preferred since disturbances due to convection were not observed with it As is commonly known normal (and allergic) sera (32 21) are resolved in the ultracentrifuge into two major peaks with sedimentation constants of the order of 4 5 and 6 5S and a minor peak of heavier material—amounting to about 3 % of the total protein—with a sedimentation constant of about 18 20S The sedimentation patterns were observed with the standard Schlieren cylindrical lens system and permanent records were obtained on photographic plates A typical sedimentation pattern in the moving partition



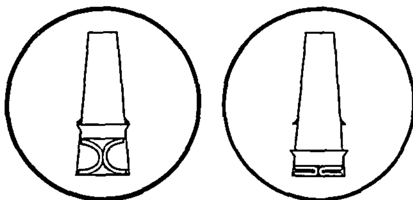


Fig 4. — Schematic representation of the fixed and moving partition cells The lower left picture represents the cells at rest and the lower sight picture represents the cell during centrifugation

cell is shown in Fig 5 In most experiments the sera were diluted with physiological saline prior to centrifugation.

In these experiments the peak corresponding to the heavy serum component(s) was allowed to sediment from the upper into the lower compartment As soon as it had crossed the partition the rotor was stopped and the serum fractions were withdrawn from each compartment for determination of skin sensitizing blocking and hemagglutination titers In a preliminary experiment centrifugation was continued until all three peaks had migrated into the bottom compartment The top compartment was found to be devoid of any of these factors and this is considered to be an

independent confirmation that these factors are associated with materials with molecular weight higher than that of serum albumin In another experiment performed in the cell with the fixed partition the lower compartment was filled with normal serum and the upper compartment with a



FIG 5 — Ultracentrifugal pattern of allergic serum in the moving partition cells The first and the last frames were photographed at 5 000 R.P M the second third and fourth frames were photographed ar 19 26 and 31 minutes respectively after the rotor attained full speed

serum from a non treated allergic individual Centrifugation was stopped when the heavy component (18 20S) had migrated into the lower compartment Both skin sensitizing and hemagglutination abilities were associated only with the bottom fraction This was a clear indication that both skin sensitizing antibodies and the hemagglutination factor(s) migrated with the heavier component

In all other experiments listed in Table III the cell was filled throughout with the same serum As can be seen from Table III with allergic sera containing no blocking antibodies skin sensitizing antibodies and the hemagglutination factor(s) were always found together in the lower compartment With heat inactivated sera no skin sensitizing antibody was found in either of the compartments however the hemagglutination factor persisted in the lower compartment With sera of treated allergic individuals it was shown that whilst the skin sensitizing antibody migrated into

serum and that this factor as well as blocking antibodies are associated with the 6 5S component To confirm unequivocally this conclusion the sera from two immunized non allergic volunteers devoid of skin sensitizing antibodies were separated by centrifugation In both cases the hemagglutination factor was found in the two compartments Thus it is fairly safe to conclude that during desensitization a hemagglutination factor with distinct molecular properties is produced i e its sedimentation constant is about 6 5S whereas that in nontreated allergic sera has a sedimentation constant of $\sim$ 16 5S (*)

(*) Since sedimentation constants were not obtained for different concentrations extrapolation of these values to zero concentration was not possible The sedimentation constants determined for the heavy component were approximately 16 5S and one would expect these values to be even larger at infinite dilution

TABLE III

Hemagglutination and PK titers of serum fractions obtained by ultracentrifugation*

SERUM	FRACTION	HEMAGGLUTINATION TITER	PK TITER
1 S**	Top Bottom	2 64	1 100
1 S	Top Bottom	not tested not tested	no reaction 1 000
1 S (heated)	Top Bottom	no reaction 32	no reaction no reaction
2 S	Top Bottom	± 64	± 1
3 B***	Top Bottom	50 200	no reaction no reaction
4 B***	Top Bottom	64 256	no reaction no reaction
2 S B+	Top Bottom	200 100	no reaction 100
2 S B (heated)	Top Bottom	2 000 256	no reaction no reaction

Titers are expressed as the reciprocal of the highest dilution still giving a positive reaction These titers are only relative No comparison with the original undiluted whole serum is made S represents sera containing skin sensitizing antibodies B represents sera containing blocking antibodies

Similar results were obtained in five experiments done with this serum

These are sera obtained from normal volunteers immunized with ragweed

+ Blocking titers were 16 and 32 for the top and bottom fractions respectively

d) The mechanism of the hemagglutination reaction

The experiments with precipitating antibodies suggest that in principle the mechanism of the hemagglutination reaction is similar to that of the precipitin reaction The agglutination of sensitized red cells may be considered to be due to their being cross linked into a three dimensional

gel by divalent antibody molecules The inhibition of the agglutination with free soluble antigen lends further support to this belief To prove unambiguously this claim one would have to succeed in inhibiting this reaction with antibody in excess and to show that the reaction would not occur with truly univalent antibody Unfortunately inhibition in antibody excess does not occur readily even in ordinary precipitin reactions (*) and up to the time of writing the present paper we have not been able to

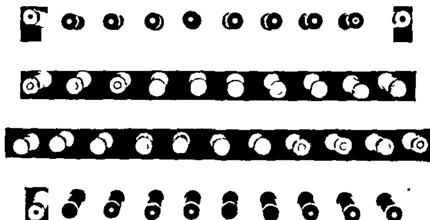


FIG 6 — N 1 and 4 represent controls
The tubes in the first row contain cells sentisized with rabbit anti ragweed antibodies in diluent The tubes in the 4th row contain non sensitized cells in ragwees colution In the row 2 and 3 positive reactions have been obtained with cells sensitizes with rabbit anti ragweed antibodies The antigen (WSR) was in solution and was added in serial halving dilutions (the maximum concentration was in the outermost tube on the lefthand side)

produce univalent antibody (**) However we have obtained further evidence for the similarity between the hemagglutination and precipitin reactions by reversing the experimental conditions i e by coupling precipitating antibodies to red cells and adding the antigen in varying amounts to a series of tubes containing a constant amount of antibody coated red cells The results of these experiments illustrated in Fig 6 closely resemble the patterns of Fig 2 and the gradation of the resulting patterns follows at least qualitatively the characteristics of a precipitin curve i e the extent of aggregation increases at first with increasing amounts of antigen (antibody excess region) reaches a maximum (optimum zone)

(*) This prozone effect has been recently studied in detail by Nisonoff and Winkler (59)

(**) We intend to prepare univalent antibodies by enzymatic degradation of precipitating antibodies If the view presented here is correct these preparations should inhibit both the precipitin and hemagglutination reactions and should still be capable of neutralizing the antigen

and finally decreases in excess antigen (*) In consequence we feel inclined to consider the hemagglutination reaction obtained with allergic sera as being due to divalent antibodies and that—as stated in Section II (*b*)—these factors have previously escaped detection by ordinary immunologic methods on account of their low concentration (**)

Comparison of hemagglutination titers with the titers obtained by ring and/or Oudin tests for precipitating antibodies offers an indirect but plausible proof for this claim As shown in Table I, hemagglutination *titers ranged from 10^4 10^7 whilst the titers of the same sera by ring or* Oudin tests were not higher than 64 or 128 One may therefore conclude that the sensitivity of the hemagglutination test is about 10^3 10^5 higher With allergic sera the highest hemagglutination titers were of the order of 10^2 10^3 i e about 10^2 10^4 lower than the titers obtained with antisera produced in experimental animals Assuming then that the nature of the hemagglutination reaction with both allergic and animal sera is the same one could hardly expect to detect any visible aggregation on addition of soluble allergens to allergic serum

Boyden s technique (52) of adsorbing protein antigens on the red cells treated with tannic acid had been applied within the last few years by a number of workers (53 54) to ragweed anti ragweed system These workers have been able to demonstrate antibodies in allergic sera with varying degrees of success*** Although no doubt this technique is highly versatile and sensitive we feel that its main drawback is that the antigens are attached to red cells only by relatively weak adsorption forces and not by stable covalent bonds The mechanism of the hemagglutination reaction is probably identical in the Boyden technique and in the technique described in this paper However since in our method ragweed antigens were coupled by azo bonds no antigens could have dissociated spontaneously from the sensitized erythrocytes as was shown to be the case with Boyden s technique (55) This is the main reason in the writer s opinion for the higher sensitivity achieved in the studies presented here in comparison

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(*) In these experiments only γ globulin fractions of rabbit antisera were used These experiments could be performed only with extremely rich antibody preparations since presumably with weaker preparations the red cells were coated primarily with non antibody globulins Experiments are under way to isolate pure and enriched antibody preparations by fractionation of antisera on homologous antigen polystyrene conjugates

(**) The plausibility of this assumption is borne out by the ultracentrifugal studies All the serum components which have a sedimentation constant of about 18S represent only about 3 % of the total serum proteins and one could therefore safely predict that skin sensitizing antibodies represent only a small fraction of these heavy components As a matter of fact preliminary quantitative ultracentrifugal results indicate that the amount of material which is removed from the heavy component by absorption of allergic sera with a ragweed polystyrene conjugate is negligible

(***) A more detailed account of the application of this technique to sera from ragweed allergic individuals is presented elsewhere (39)

(****) These complications are probably minimized when the antigens used for coating tanned erythrocytes are large molecular weight proteins since desorption

Feinberg et al (54) that complete desensitization of a site of normal skin sensitized with allergic serum could not be achieved with tanned stromata coated with ragweed components

For the hemagglutination techniques the sensitized red blood cells are necessary only to provide the bulk which through cross linking with antibodies will lead to visible aggregation For the full understanding of the mechanism of hemagglutination reaction it is essential to establish the minimum number of antibody molecules per sensitized erythrocyte

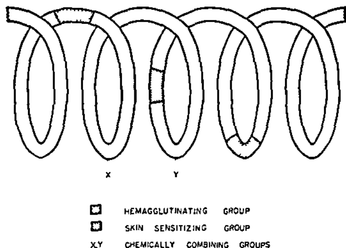


FIG 7 — Configuration of a hypothetical molecule endowed with hemagglutination and skin sensitizing characteristics

which will still lead to agglutination So far preliminary experiments indicate that 10 100 antibody molecules per sensitized red cell are sufficient to give a discernible titer* In the hemagglutination experiments with rabbit ragweed antibodies coupled to erythrocytes as little as 10^{-7} mg of ragweed protein yields a visible reaction In comparison the sensitivity of the agar gel technique is lower i e it is claimed (62) that this technique will detect 10^{-3} 10^{-4} mg of antigen

The fact that skin sensitizing activity may be destroyed by heating without impairing the hemagglutinating ability may lead one to believe that in non treated sera these are two independent properties associated with two distinct types of molecules Nevertheless the possibility that both these factors are associated with one and the same molecule cannot be excluded on the basis of the results of the various fractionation procedures This supposition can be justified on terms of a hypothetical protein molecule containing both these factors as illustrated in Fig 7 Thus the two dotted regions would represent portions of the molecule which are sterically *complementary with respect to the antigenic groupings in ragweed and*

will be then more difficult on account of the greater number of links between the protein and red cells

(*) Quantitative experiments with I_{131} labelled antibodies and antigens are under way to establish this more definitely

the lined portion would represent the grouping which has the ability to become fixed to skin and tissues i e the part of the molecule mediating skin sensitization The groups X and Y would represent chemically reactive portions such as SH groups, which on heating may condense to lead to an irreversible change in the configuration of the protein molecule Thus the grouping responsible for skin sensitization without necessarily being destroyed during heating (although this may also occur) may become completely shielded i e its attachment to the skin may be blocked and thus its ability to sensitize the skin may be inhibited This change, however may occur without affecting the ability of the other two groupings to combine with ragweed allergens which are coupled to erythrocytes or to polystyrene Similarly in view of our inability to separate blocking activity from hemag glutinating capacity in the same fractions of treated serum one may suggest that as with skin sensitizing antibodies these two different attributes are different manifestations of one and the same molecule and that blocking antibodies may be regarded as normal antibodies produced in response to immunization To substantiate this proposal we have shown that antisera to ragweed produced in rabbits goats and dogs had not only the ability to hemagglutinate sensitized red cells but could also block the reaction of ragweed allergens in human skin sensitized with reagin containing serum Hence one may consider that blocking activity is the result of combination between antibodies and ragweed and that the latter is thus inactivated In this paper hemagglutination is considered to be due to combination of these antibodies with ragweed constituents coupled to erythrocytes Since hemagglutination is still exhibited by non treated allergic sera even after heat inactivation of their skin sensitizing ability one would expect that these sera should possess also blocking activity* The fact that no blocking activity has ever been reported to exist in non treated sera (after heating) may be due to its being present below the threshold level required for its detection by the *in vivo* test This interpretation is offered on the basis of the following experimental results Three normal individuals were immunized with ragweed None of the sera contained skin sensitizing antibodies However hemagglutination activity was found in all three sera in varying titers i e in dilutions of 64 000 2 048 and 128 Blocking activity could be demonstrated by the *in vivo* test only in the serum with the highest hemagglutination titer (hemag titer=64 000 blocking titer=64) The γ globulin fractions of the other two sera were then concentrated five fold and on retesting these concentrated fractions blocking activity was indeed demonstrated in both cases and the hemagglutination titers had also increased**

On the other hand if no blocking activity is revealed by non treated sera after heating then one would be inclined to assume that the groupings responsible for hemagglutination ability of the skin sensitizing antibody on the one hand and of the blocking antibody on the other are complementary to different portions of the ragweed molecule(s) This is in agreement

(*) This effect should be exhibited irrespective of whether the groupings responsible for hemagglutination and skin sensitizing activities reside on the same or on different molecules

(**) Non treated sera from ragweed sensitive individuals are being tested for blocking activity by the same procedure

with the findings (60 61) that ragweed contains a multiplicity of antigens

duals directed against different antigenic constituents in ragweed (44) and 2°) during desensitization a new type of reagin(s) may be produced to a dialyzable ragweed fraction and to which apparently no skin sensitizing antibodies are produced spontaneously by non treated allergic individuals (45) This of course is not surprising considering the chemical complexity of ragweed pollen and the somewhat similar findings of Kuhns (46) who has shown that three types of antibody to diphtheria toxoid may be pro duced The diversity of antibodies to ragweed allergens with regard to their sedimentation constants would indicate that different mechanims of antibody formation must be responsible for their production A similar suggestion has been made in a review article by Taliaferro (47) for Forssman antisheep red cell antibodies produced in rabbits which have been found both with the low and the high molecular weight serum components As regards antibodies found in the heavier globulin fraction one may also cite Rh antibodies (48) Wasserman antibodies (49) factors present in sera of patients with rheumatoid arthritis which may be involved in the sheep cell agglutination reaction (50) and auto antibodies to thyroid (51)

SUMMARY

The methods for characterization and detection of antibodies in sera from ragweed sensitive individuals are reviewed

The weight of evidence suggests that skin sensitizing antibodies migrate electrophoretically as γ_1 globulins and that blocking antibodies are asso ciated primarily with γ_2 globulins By ultracentrifugation skin sensitizing antibodies have been shown to be in a heavy globulin fraction (sedimentation constant 16 5S) whilst blocking antibodies are found in the normal globulin fraction (6 5S)

The use of antigen coated erythrocytes has led to the development of a highly sensitive and specific method for the detection of antibodies in sera of ragweed sensitive individuals The factors reponsible for hemaggluti tination are considered to have properties similar to those of ordinary divalent antibodies These factors are found in all serum fractions contai ning skin sensitizing and/or blocking antibodies The possible nature of antibody like factors found in allergic sera are discussed

RÉSUMÉ

L auteur passe d abord en revue les methodes permettant de deceler et de caracteriser les anticorps dans les serums des individus sensibilises au Ragweed (Ambrosia) Des preuves importantes sont apportees demon

trant que l anticorps sensibilisateur de la peau migre électrophoretiquement comme une γ_1 globuline et que l anticorps bloquant se déplace essentiellement avec la globuline γ_2

Par la methode d ultracentrifugation l anticorps sensibilisateur de la peau se révele comme etant une fraction globulinique lourde (constante de sédimentation > 16 5 S) alors que l anticorps bloquant est retrouve dans la fraction globulinique normale (6 5 S)

L emploi d hematies enrobees avec l antigene a fourni une methode sensible et spécifique pour la detection des anticorps dans les serums des individus sensibilises au Ragweed. Les facteurs responsables de l hémagglutination passive peuvent etre considérés comme ayant des propriétes similaires aux anticorps ordinaires bivalents On trouve ce type d anticorps dans toutes les fractions seriques contenant des anticorps sensibilisants de la peau qu il y ait ou non des anticorps bloquants La nature des anticorps que l on trouve dans le serum des allergiques est discute

ZUSAMMENFASSUNG

Die Methoden zur Charakterisierung und Entdeckung von antikorperahnlichen Faktorem im Serum von gegen Ambrosia uberempfindlichen Personen werden gepruft

Die Ergebnisse zeigen dass die haut sensibilisierenden Antikorper in der Elektrophorese mit den γ_1 Globulinen und die blockierenden Antikorper hauptsachich mit den γ_2 Globulinen wandern Beim Ultrazentrifugieren zeigte es sich dass die Haut sensibilisierenden Antikorper sich in einer schweren Globulinfraktion befinden (Sedimentationskonstante > 16 58) wahrend die blockierenden Antikorper sich in der normalen Globulinfraktion (6 58) vorfanden

Faktoren scheinen ahnliche Eigenschaften wie die einfachen divaltenten Antikorper zu besitzen Diese Faktoren fanden sich in allen Serumfraktionen die Haut sensibilisierende und/oder blockierende Antikorper enthalten Die mogliche Natur der in Allergie Seren vorgefundenen Antikorper ahnlichen Faktoren wird diskutiert

RESUMEN

El autor hace una revision de los metodos que permiten reconocer y detectar en el suero de pacientes sensitivos a «ragweed» ciertos componentes con propiedades semejantes a los anticuerpos

La evidencia acumulada indica que los anticuerpos sensibilizantes de la piel migran electroforéticamente junto con las γ_1 globulinas en tanto que los anticuerpos bloqueantes están asociados especialmente con las γ_2 globulinas Por ultracentrifugacion se ha demostrado que los anticuerpos sensibilizantes de la piel se encuentran en una fracción globulinica pesada

(constante de sedimentacion mayor de 16 58) mientras que los anticuerpos bloqueantes se encuentran en la fracción globulinica normal (6 58)

Mediante el test de aglutinacion utilizando glóbulos rojos sensibilizados con antígeno se ha podido poner a punto un metodo especifico y de alta sensibilidad para la busqueda de anticuerpos en el suero de pacientes sensibles a «ragweed» Los factores responsables de la aglutinación tienen propiedades similares a los anticuerpos comunes divalentes y se encuentran en el suero de pacientes con anticuerpos sensibilizantes o bloqueantes indistintamente El autor discute la posible naturaleza de estos factores

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SYMPOSIUM III

Acquisitions récentes sur l'étiologie et le traitement des affections allergiques

Recent advances in some phases of clinical allergy

Neue Ergebenisse uber die Aetiologie und die Behandlung der allergischen Krankheiten

Recientes adelantos en la etiologia y tratamiento de las enfermedades alérgicas

INTRODUCTION

par

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Devant l ampleur et la diversité des sujets traités par les differents orateurs nous nous bornerons a signaler ici les aspects les plus interes sants des rapports presentes a la lumiere de notre experience personnelle

Parmi les acquisitions les plus recentes concernant *l etiologie des affec tions allergiques* un des problemes les plus importants est sans aucun doute celui des *reactions aux medicaments* Ce sujet qui sera traite par E A Brown et par M Samter s impose aujourd hui a l attention et a la reflexion non seulement des specialistes de l allergie mais de tous les medecins praticiens On est veritablement en droit d affirmer qu il s agit la d un probleme *d ordre general*

C est un fait que le nombre toujours croissant de medicaments nous a permis d assister a l éclosion de nombreuses reactions aux medicaments presentant des aspects cliniques fort differents A des observations deja connues d autres completement nouvelles se sont ajoutees Les lesions anatomo pathologiques survenues dans certains cas ont pu etre etudiees des mesures ont ete envisagees concernant la prevention et la therapie et enfin l on a examine a nouveau le mecanisme pathogenique de ces manifestations En d autres termes il s est constitué un nouveau chapitre des Sciences médicales lequel a l encontre de celui concernant la patho logie spontanee pourrait etre nomme celui de la « pathologie provoquee » (pathologie dite iatrogene »)

Ces manifestations (cutanees hematologiques viscérales et generales) qui sont causees par ces substances dont on attend au contraire des effets favorables sur l évolution d une forme pathologique determinée se presentent de façon inopinee avec des caracteres heterogenes qui les rendent difficilement identifiables Il est donc parfois difficile de poser un diagnostic le pronostic comme la prescription d une therapeutique adequate peuvent s averer egalement particulierement difficiles

Les reactions aux médicaments apparaissent comme un probleme tres important si l on considere leur frequence Cette fréquence qui est toujours elevee mais qui varie suivant les medicaments est difficile a evaluer avec exactitude De nombreux cas echappent en effet aux statis

tiques soit parce que les manifestations survenues etaient insignifiantes et que le malade ne croit pas utile d en parler au medecin soit parce que le medecin lui meme etant donne leur caractere de banalite ne juge pas necessaire de les signaler soit enfin parce que dans le cas d une issue fatale il apparait inutile d attirer l attention sur l incident Il faut ajouter que les données de la littérature ne sont pas toujours exactes car il ne faut pas oublier que l on attribue parfois a un medicament une action qu il n a point determinee Il suffira a ce propos de rappeler quelques cas ou l'étiologie exacte n a pas pu etre precisee d apres Nasser et Caroli la plupart des icteres qui surviennent a la suite de traitements par la chlorpromazine et qui lui sont generalement attribués seraient au contraire dus a des hepatites virales ou à des icteres par serum homo logue les reactions au vaccin antigrippal peuvent etre attribuées a une sensi bilite aux constituants normaux de l œuf dans lequel le virus est cultive (nous rappelons a ce propos que « l American Foundation for Allergic Disease » a cru bon par la publication d un avis d attirer l attention de tous les medecins sur le danger que le vaccin peut constituer pour des sujets sensibles aux œufs) les réactions produites par des vaccins filtres sur soie peuvent elles memes etre engendrées par la sensibilite particuliere de certains individus à la soie (Friedman et coll Coleman etc)

Il faut ajouter — et je voudrais attirer l attention sur ce point — que les phenomenes reactionnels aux médicaments semblent toujours en augmen tation Cette affirmation meme si elle n est pas etayée par des statistiques precises est confirmee cependant par la frequence toujours plus grande d observations cliniques et également par le fait que dans le monde la production et la consommation des medicaments ne cessent de croitre (di Mattei) Il nous semble egalement opportun de signaler a ce sujet que l augmentation tres sensible de certaines formes morbides — en parti culier celles groupées dans le cadre de « maladies du collagene » — observée au cours de ces dernieres années peut certainement etre attribuee a l emploi de certains médicaments Dans la périartente noueuse l impor tance etiologique que peut revetir le traitement par le sérum l iode les sulfamides est bien connue Le lupus erythémateux hydralazinique avec cellules de Hargraves signalé en 1953 par Morrow et collaborateurs chez des sujets hypertendus et traites par ce medicament a éte par la suite confirme par différents auteurs et meme reproduit experimentalement

Un des aspects de cette question que je voudrais évoquer car on en discute encore c est celui de la classification et de la terminologie des modalites reactionnelles aux medicaments

Tout en nous rendant compte des grandes difficultes inherentes a toute tentative de classification et sans esperer pouvoir englober tous les cas cliniques qui peuvent se vérifier en pratique il nous semble cependant opportun pour mieux orienter la discussion de distinguer entre 1°) les symptomes qui rentrent dans le cadre des actions pharmacologiques exer cées par les médicaments 2°) les symptomes qui sont le plus souvent révelateurs d une reactivité particuliere de l organisme On se doit d envisa ger separement ces deux groupes de symptomes qui exigent aussi des thérapeutiques différentes bien que parfois ils se présentent associes entre eux rendant ainsi fort difficile l interpretation exacte de la manifestation clinique

1° *Symptômes qui rentrent dans le cadre des actions pharmacologiques exercees par les medicaments* ce genre de symptomes qui apparaissent toujours chez des sujets presentant un terrain individuel particulier peuvent se ramener a mon avis a des mecanismes pathogeniques differents et peuvent se grouper de la façon suivante

a) Des manifestations analogues a celles provenant d une dose excessive du médicament Cette symptomatologie qui est la plus fréquemment rencontree est désignée par differentes denominations « variations quantitatives de l action pharmacologique » « idiosyncrasie pharmacologique » « toxicite a dose non toxique » « relative overdosage » Les symptomes rentrent dans le cadre des proprietes fondamentales du medicament

b) Des manifestations de types différents qui relevent des actions indirectes du médicament (« secondary effects ») Elles mettent en évidence le plus souvent un état de desequilibre cellulaire Les antibiotiques par exemple peuvent engendrer des manifestations cliniques dues à une action indirecte exercée par eux sur la synthese des vitamines ou sur le developpement des germes saprophytes qui acquierent un pouvoir pathogene (« dismicrobisme latent » d apres Chini et di Raimondo candidoses broncho pulmonaires etc) L anemie mégaloblastique provoquee par les anticonvulsivants signalee notamment par les auteurs anglais et scandinaves pourrait etre classee dans ce groupe On pense en effet que cette affection pourrait decouler d une action compétitive entre certaines molecules des anticonvulsivants (contenant dans leur formule des noyaux tels que la pyrimidine et l imidazol) et l acide folique

Une autre possibilité dont on doit tenir compte dans ce domaine est celle des manifestations toxiques pouvant etre engendrees par certains dérives du médicament doues par rapport au médicament lui meme d un pouvoir toxique plus accentue Du point de vue pathogenique di Mattei a classé ces symptomes avec ceux du premier groupe comme des phenomenes lies au « metabolisme trouble » du medicament Il s agit la d un nouveau domaine de recherches susceptible de se developper ulterieurement puisque ces symptomes sont probablement beaucoup plus varies que ceux que nous connaissons actuellement

2° *Symptômes qui temoignent le plus souvent d une reactivite particuliere de l organisme* (variations qualitatives de l action pharmacologique) Ces reactions qui ne rappellent pas les actions pharmacologiques directes et indirectes du medicament sont caractérisees par l apparition de manifestations morbides présentant souvent l aspect des formes allergiques reconnues (reactions immédiates réactions retardees auto sensibilisation)

Dans la sphere de l allergie on ne peut pas toutefois englober toutes les manifestations de ce type parce qu il n est pas possible de demontrer et parfois meme pas de supposer un mécanisme de reaction antigene anticorps D un interet tout particulier apparait donc l hypothèse de Lunedei selon laquelle l ensemble des manifestations de ce groupe est designé par l expression de « reactivite alteree » Celles ci peuvent relever d une « reactivité alteree » par la presence d anticorps (allergique) ou une « reactivite alterée » primitive des tissus (non allergique) ou le médicament peut agir soit sur le systeme neurovegetatif soit directement sur les tissus A ce sujet il faut se rappeler qu il a eté démontré recemment que beaucoup de medicaments (morphine atropine quinine codéine arsenobenzols

etc) rentrent dans le groupe des substances histamino-liberatrices et pourraient donc par ce mecanisme determiner des manifestations du type allergique chez l homme des le premier contact avec le medicament (Paton Schachter) Dans ce cas on doit admettre d ailleurs, une facilite particuliere de l histamino liberation

Il n est pas possible étant donne la grande complexite et l ampleur du sujet

camen

st dan

genique le mecanisme allergique apparait comme suffisamment etabli mais que le *mecanisme des reactions n'est pas encore eclairci dans* les formes produites par des substances chimiques simples Dans l etat actuel de la question on peut dire que si dans certains cas assez rares comme l ont recemment souligne Halpern et collaborateurs la substance chimique simple peut se comporter comme un antigene complet il faut admettre que dans la presque totalite des cas en suivant les donnees fournies par les recherches desormais classiques de Landsteiner il se forme des complexes haptenes-proteines capables de sensibiliser l organisme Cette hypothese a été largement developpée speciale ment dans le domaine de l hematologie ou il s est ainsi crée un nouveau domaine de recherches l immunohematologie

Dans l étude du mecanisme des reactions medicamenteuses il faut se rappeler que l un des aspects les plus interessants est represente par les rapports existant entre la structure chimique de ces substances et leur pouvoir de sensibilisation Mayer a rapporte que des substances tres differentes du point de vue chimique se transforment *in vivo* en composes quinoniques doues d un pouvoir sensibilisant marque Landsteiner a demontre que les composes chimiques ayant une chaine latérale en position para meta ou ortho manifestent des proprietes sensibilisatrices differentes Nitti Bovet et Depierre ont observe que dans la serie des amines aromatiques la position « para » apparait comme particulierement favorable a la sensibilisation

L organisme peut d ailleurs se sensibiliser aussi bien a la molécule entiere qu a certaines structures chimiques de la molecule Un sujet donne, sensibilisé par une premiere substance peut témoigner d une sensibilite particuliere vis a vis de tous les composes ayant une certaine structure chimique commune (sensibilite de groupe)

En definitive on peut affirmer que beaucoup de problemes concernant *les reactions aux medicaments n ont pas encore eté resolus* C est pourquoi les recherches tendant a en deceler les mecanismes, probablement multiples et qui se poursuivent actuellement revetent le plus grand interet

Parmi les facteurs etiologiques qui sont a l origine des affections allergiques en plus des medicaments dont nous avons parle jusqu ici il faut signaler les *insectes* C est sur cette question que nous ecouterons avec le plus grand interet le rapport de S M Feinberg

Du point de vue general il faut rappeler que dans la pratique medicale on a constate depuis les epoques les plus lointaines que certains individus peuvent presenter des reactions particulieres generales et locales à la suite de piqures ou de morsures d insectes Ces reactions qui sont vraisemblablement plus fréquentes que ne le rapporte la litterature sont dues dans la

plupart des cas a un mecanisme allergique et plus exactement a une sensibilisation des allergenes contenus dans les secretions ou dans les divers tissus et organes de ces insectes On ne saurait pas exclure dans certains cas la possibilité que ces réactions du type allergique soient determinees aussi par l introduction dans l organisme de substances capables de libérer de l histamine

Il faut également souligner qu au cours de ces dernieres annees on a constaté que les insectes peuvent determiner par inhalation des mani festations nasales et bronchiques allergiques et saisonnieres dont la fréquence pourrait etre relativement grande En d autres termes l aller gie aux insectes est en train de prendre comme l affirme Feinberg une place primordiale parmi les pneumallergenes analogue a celle assignee aux pollens et aux moisissures Et voila que s ouvre aux chercheurs un vaste domaine afin de préciser l incidence dans les différents pays de cette forme particuliere de sensibilité et de decouvrir grace aux methodes les plus modernes d investigation l antigene contenu chez les insectes et les rapports qui peuvent exister entre les antigenes de differentes especes ce qui d ailleurs a deja été mis en evidence pour certains insectes

Devant l interet suscite par les manifestations allergiques déterminees par les insectes je voudrais egalement rappeler ici de tres interessantes observations faites par Marconi dans un etablissement de culture du ver a soie à Ascoli Piceno (Italie) quant a la forte capacité antigeniques des substances contenues dans le ver a soie

La succession des phases formant le cycle vital du ver a soie (Bombyx muri Linneus) est bien connue Une enquete pratiquee sur 100 ouvriers de l etablissement en question a Ascoli Piceno dans l atelier de « papillon nement » a prouve que 46 d entre eux presentaient des symptomes varies (coryza spasmodique asthme dermatoses) imputables aux substances contenues dans les papillons du ver a soie Chez de nombreux sujets on a pu prouver la positivité des épreuves cutanees et du transfert passif Il faut remarquer que ces tests ont eté effectués avec des substances provenant des trois varietes de ver a soie or chinois jaune indigene et blanc chinois D une façon generale on a constate une reaction positive a des substances des trois especes parfois pour une seule des trois On a pu egalement observer une cuti reaction positive chez certains sujets qui ne presentaient pas par ailleurs de symptomes cliniques

A ce propos il sera interessant de rappeler à titre de curiosité historique que les « graves manifestations aux yeux » dont eut a souffrir Marcello Malpighi (1628 1694) alors qu il se consacrait a son etude anatomique du ver a soie — qui devait lui servir de matiere pour son remarquable ouvrage *De bombice* — sont probablement imputables a une reaction allergique produite par les substances de cet insecte

Un autre sujet d ordre etiologique et pathogenique tres etendu et tres complexe est celui de la *psychosomatique et allergie* que traiteront ample ment H et D Miller

Il nous semble necessaire a titre d introduction de tracer a grands traits les rapports pouvant exister entre les facteurs neuro psychiques et l allergie Les facteurs psychiques peuvent ils constituer la cause qui dechaine la symptomatologie allergique ? L alterat on psychique du sujet peut elle dériver de la manifestation clinique d ordre allergique ? Les

influences psychiques peuvent elles représenter des facteurs généraux de predisposition aux syndromes allergiques ?

Si nous envisageons le premier de ces problemes il faut preciser deux eventualités possibles

La premiere est que le stimulus neuro psychique est capable d en gendrer par lui meme la symptomatologie Une semblable possibilite rentre dans la theorie designee par le terme de « psychosomatique » Il faut rappeler a ce propos que contrairement aux conceptions neuro physio logiques qui accordent aux stimuli emotifs une simple action générale la théorie psychosomatique les considere comme capables de susciter par eux memes des répercussions somatiques bien definies Suivant les defen seurs de cette doctrine on pourrait meme parvenir a l affirmation que cer tains syndromes allergiques trouvent leur origine uniquement dans des conflits émotionnels C est ainsi que l asthme pourrait etre considére comme l expression morbide exterieure de la crainte de perdre l amour maternel ou des conflits d ordre familial C est au meme mecanisme qu il faudrait imputer les nombreux cas de periarthrites de l epaule rapportés par Ferond de Bruxelles à la suite des bombardements de la derniere guerre mondiale

En ce qui concerne cette théorie il faut avant tout remarquer que les modalites selon lesquelles les stimuli psychiques provoqueraient la reponse pathologique à travers les structures neuro végétatives centrales et periphériques apparaissent comme extremement complexes Il faut preciser ici que les recherches neurophysiologiques de ces dernieres années nous ont amenes a admettre que la regulation neuro vegetative se fait soit a la peripherie (dans les différents tissus) soit dans les différents centres nerveux moelle bulbe mesencephale diencephale et meme cortex cere bral Ceci pourrait nous amener a affirmer suivant l expression de Dell, que meme « les parties les plus evoluées de l encephale sont au service des grandes regulations végétatives » Dans ce domaine il faut particulierement rappeler les recherches qui ont mis en lumiere la presence du systeme auto nome dans les structures corticales Ces recherches largement confirmees chez l homme par les observations de Penfield et Jasper de Kaada ont permis de preciser le role des systemes subcorticaux de correlation parmi lesquels le systeme reticulaire ascendant de Moruzzi et Magoun revet une importance particuliere

Il faut souligner ici que le système nerveux végétatif peut agir sur les tissus non seulement à travers des mecanismes d un caractere général (modi fications de l activite endocrine variations de l equilibre electrolytique ou acido basique) mais aussi par action indirecte soit vaso motrice soit trophique (Pour ces derniers il y a egalement lieu de rappeler les donnees sur lesquelles se basent les courants idéologiques neuro relationistes Reilly Speransky)

D apres Lunedei et Belloni les stimuli d ordre psychique peuvent reve tir une telle intensite jusqu a determiner par eux memes la reaction pathologique (phenomene pathologique *cree* par l action nerveuse) ou alors etre simplement revélateurs d une disposition particuliere du tissu lesé (phénomene pathologique *revelé* par l action nerveuse) Si le premier cas est tout a fait exceptionnel le deuxieme se rencontre beaucoup plus facilement

Éventuellement le syndrome peut apparaitre chez des sujets souffrant deja d une affection allergique provoquee d ailleurs par des facteurs differents Dans des cas de ce genre un stimulus psychique agissant probablement à travers un mécanisme de reflexe conditionné peut etre en mesure de provoquer une crise paroxystique comme elle peut rendre durable une crise en cours (crise d asthme durable par « psychisme »)

Quant au second probleme — a savoir si la symptomatologie psychique du sujet peut etre influencée par la maladie — il est necessaire de pre ciser que les repercussions neuro vegetatives et psycho affectives des reactions peripheriques sont d ordre organique ou meme dans certains cas d ordre allergique (Werner) et dependent des caracteristiques ana tomo physiologiques de l organe touche du pouvoir reflectogene de certai nes structures et du cours de la maladie

Les influences psychiques enfin peuvent aussi representer des facteurs généraux de prédisposition aux syndromes allergiques Cette possibilite est basee sur les recherches concernant la personnalite de l individu comme egalement sur des situations psychiques particulieres pouvant favoriser la sensibilisation

Un *probleme particulier d ordre eminemment « pathogenique » est* celui qui sera discute aujourd hui par S Bukantz et concernant *l immuno chimie du sputum des asthmatiques*

Les recherches conduites dans ce sens peuvent revetir un interet parti culier si on les considere du point de vue physiopathologique de l obstruc tion bronchique diffuse telle qu elle se verifie dans l asthme bronchique durable dans lequel l element fondamental est justement represente par l hypersécrétion bronchique Il faut rappeler à ce propos que de nombreux auteurs en se basant sur des observations anatomo pathologiques de malades decedes au cours d une crise d asthme ont porte leur attention non seulement sur l eosinophilie ou sur les alterations de l epithelium bronchique mais aussi et surtout sur l hypertrophie des glandes de la muqueuse et sur la production excessive de sécrétion visqueuse tres parti culiere en leur attribuant une importance preponderante en tant que cause *de la mort* Rackemann a emis *l hypothese suivant laquelle « la lesion primi tive* serait representee par un trouble de l activite secretoire bronchique »

Une etude approfondie et etendue de la secretion bronchique chez les asthmatiques pourrait eclairer certains aspects étiopathogénetiques des formes d asthme graves et particulierement de ces formes qui repondent mal aux *therapies habituelles et qui aboutissent dans un laps de temps tres* court a une issue fatale (souvent en 2 ans) et que nous avons propose de designer sous le nom d asthme « malin » Une pareille recherche peut en outre offrir un interet pratique therapeutique en indiquant les possibilites thérapeutiques des aerosols d enzymes aptes a reduire la viscosite particu liere des secretions bronchiques

Un des aspects du probleme dont nous parlons ici est celui de preciser éventuellement chez les asthmatiques les rapports pouvant exister entre les alterations de la secretion bronchique et la secretion pancreatique (pos *sibilite prouvée par les observations de Riva et Probst) A ce propos on* connait, bien l existence d alterations associees des glandes du pancreas et des bronches et celles des glandes sudoripares et salivaires (Artom di

Sant Agnese) — Ces formes cliniques se rencontrent particulierement chez les enfants et on les nomme « *Mucoviscidose* » (ou aussi *Fibrose pancreatique avec bronchiectasies d origine familiale* ou *Dysporia entero broncho pancreatica*)

En nous reférant aux *acquisitions les plus recentes dans le domaine de la therapeutique des affections allergiques* nous pouvons observer que nous nous trouvons actuellement dans une phase assez stationnaire dans le sens qu il n y a pas eu au cours de ces dernieres années de nouvelles orientations dans la recherche et dans la thérapeutique de l importance de celles de la découverte des antihistaminiques de synthese (Bovet Halpern) de l A C T H et de la cortisone (Hench et collaborateurs) et qui ont influence de façon si décisive la physiopathologie et la therapie des affections allergiques Il faut cependant remarquer que la *therapeutique par les hormones* qui fera l objet du rapport presenté par P H Forsham apparait encore aujourd hui du plus haut interet theorique et pratique

En ce qui concerne spécialement la therapeutique par des hormones il faut préciser que outre les cas bien definis d une perturbation hormonale elle est egalement employee dans ces cas cliniques particuliers ou il est possible de démontrer une sensibilisation aux hormones (hyposensibilisation specifique Zondek et Bromberg Biozzi Serafini et Malizia Pasteur Vallery Radot etc)

Au cours de ces dernieres annees l usage des hormones cortico surrenales s est tellement repandu qu il a fini par provoquer une certaine inquiétude et une certaine perplexite A cet egard il est bon de partager l orientation prise au cours des récents Congres et reunions consacrés a cette question et qui recommande de n employer ces produits que d une façon limitee et seulement dans des cas ou l indication apparait précise

En ce qui concerne l A C T H sans nous arreter sur les recherches par ailleurs remarquables que l on consacre actuellement a son activité biologique chez l homme ni sur les derives a action prolongee je me bornerai a signaler que si l on a rapporté un nombre toujours croissant de réactions anaphylactiques un phenomène opposé a éte mis en évidence que Forsham et Renold ont dénomme « *resistance a l A C T H* » Ce phénomene consiste en l absence d une reponse clinique et metabolique de l organisme apres l injection de l A C T H pratiquée par voie intramusculaire alors que chez les memes sujets on obtient une reponse positive lorsque l A C T H est administre par voie intraveineuse Nous avons decrit des cas analogues et ce phénomene a ete défini par nous comme « inefficacite de l A C T H administre par voie intramusculaire » (Serafini et coll) Dans un cas nous avons pu constater egalement l influence d un autre élément le siege de l injection Nous avons en effet observe que la réponse à l A C T H etait absente si l injection était pratiquée dans les muscles fessiers alors qu elle réapparaissait si elle etait pratiquee dans le muscle deltoide (« résistance d origine tissulaire locale »)

En ce qui concerne les steroides de la surrenale il faut signaler que leur emploi est devenu toujours plus répandu apres l introduction en therapeutique des dérivés synthétiques de la cortisone et de l hydrocortisone et la possibilité d administrer certains d entre eux par voie parentérale Dans le cas d une maladie prolongee et d un emploi continu de ces medi

caments il se pose pour le médecin traitant le problème important des effets d'un traitement prolongé étant donné la complexité des altérations physio-pathologiques pouvant se vérifier en de semblables circonstances

Il faut rappeler ici qu'au cours d'une thérapie conduite avec des doses relativement importantes de ces produits et pour une période de temps assez longue il est possible d'observer parfois ces manifestations bien connues que l'on désigne sous le nom de « hypercorticisme » (Slocumb et coll.) et d'autre part des phénomènes reliés à une insuffisance partielle ou totale de la cortico-surrénale. A ce propos il est important de signaler que l'insuffisance cortico-surrénale peut donner lieu assez souvent à des *accidents d'une certaine gravité pouvant avoir parfois une issue fatale et* qui sont dus à une atrophie des surrénales. A côté de ces cas d'une gravité exceptionnelle et au cours desquels l'insuffisance cortico-surrénale se manifeste de façon dramatique il en est d'autres beaucoup plus nombreux où les manifestations de l'insuffisance cortico-surrénale présentent des caractères d'une gravité atténuée au point de pouvoir passer inaperçues et nécessitant pour les mettre en évidence un examen approfondi de la fonction cortico-surrénale

Je voudrais enfin signaler ces manifestations cliniques qui ont été dénommées par Slocumb « panmesenchymal reactions » (type Lupus Frerichs) ou « Panangitis » (type polyartérite noueuse Kemper et collaborateurs) peuvent apparaître au cours du traitement par la cortisone ou ses dérivés administrés à des doses excessives ou lors de la réduction des doses ou encore dans le cas d'une interruption brusque du traitement. Il est à remarquer que (comme l'ont affirmé Kemper et collaborateurs) ces manifestations apparaissent presque exclusivement chez des malades atteints de polyarthrite chronique évolutive

Qu'il me soit permis mes chers et illustres Collègues en terminant ce rapport de préciser à nouveau que dans cet exposé je me suis borné à indiquer d'un point de vue tout à fait général les différents sujets mis en discussion sans entrer dans les détails puisque chacun d'eux sera traité avec compétence et savoir par un spécialiste de la question.

C'est au nom de tous les participants que je leur adresse l'expression de notre reconnaissance d'avoir bien voulu apporter à l'examen des sujets mis en discussion d'une indéniable importance et d'une brûlante actualité la précieuse contribution de leur savoir et de leur enthousiasme

RÉSUMÉ

Dans ce rapport l'auteur souligne les points les plus importants traités par les différents orateurs

Dans le domaine des affections allergiques l'auteur examine 1° les réactions aux médicaments en mettant en relief l'augmentation de leur gravité et de leur fréquence et en faisant mention d'une classification et de leur mécanisme pathogénique 2° les insectes en tant que facteurs importants dans les manifestations allergiques respiratoires par inhalation 3° la

psychosomatique en traçant a grands traits les rapports pouvant exister entre les facteurs neuropsychiques et l allergie

L auteur traite ensuite brievement le probleme particulier — d un interet eminnemment pathogénique — de l immunochimie de l expectoration chez les asthmatiques en soulignant l interet que peuvent revetir de telles recherches sous l angle physiopathologique de l obstruction diffuse des bronches observee dans l asthme bronchique

En se referant aux acquisitions les plus recentes dans la therapeutique des affections allergiques et apres avoir noté que l on se trouve actuellement dans une phase stationnaire du progres dans ce domaine l auteur souligne l importance acquise aujourd hui par la therapie par les hormones A ce propos il evoque la possibilite d une therapie efficace par la desensibilisation spécifique dans certains cas d hypersensibilite aux hormones sexuelles femelles L auteur attire l attention sur certains aspects physiopathologiques se rattachant a l emploi de l A C T H de la cortisone et de ses derives en montrant leur interet du point de vue clinique et therapeutique

SUMMARY

In this report the author points out the most important features of the subjects with which the various speakers have dealt. In the field of allergic

2° The part played by insects as important inhalant factors of allergic disturbances

3° The importance of the psychosomatic factors and the relationship between neuro psychic phenomena and allergy

The author then briefly deals with the particular notion of the immuno chemistry of sputum which bears a high pathogenetic interest in relation with the physio-pathology of the diffuse bronchial obstruction in asthma

Referring to the latest therapeutical advances for the allergic diseases and after having remarked that at the time being progress in this matter is at a standstill the author lays stress on the importance that hormonal therapy has gained today In regard to this after having mentionned the action on hormonal disturbances and the possibility of an effective specific desensiti zation therapy in certain cases of hypersensitivity to female sexual hormones the author draws the attention on certain physiopathological aspects con nected with the use of A C T H and of cortisone and its derivatives thus giving evidence as to their interest from the clinical and therapeutical point of view

ZUSAMMENFASSUNG

In diesem Bericht werden die wichtigsten die von verschiedenen Rednern behandelte Materie betreffenden Aspekte hervorgebracht

Der Autor untersucht auf dem Gebiet allergischer Affektionen 1 Die Reaktionen gegenuber Medikamenten indem er die bestandige Zunahme der Erkraukuugsgraviditat und die wachsende Frequenz hervorhebt und

eine Klassifikation und ihren pathogenetischen Mechanismus erwahnt 2 Die Insekten als bedeutende Faktoren fur durch Inhalation zustande kommende allergische Respirationsmanifestationen 3 Die Psychosomatik indem er in grossen Zugen die moglicherweise existierenden Zusammenhange zwischen neuropsychischen Faktoren und der Allergie aufzeichnet

Anschliessend behandelt der Autor kurz das besondere Problem der Immonochemie der Expektoration bei Asthmatikern — was von immenser pathogenetischer Bedeutung ist — indem er das Interesse betont welches solche Untersuchungen unter dem Aspekt des Problems des physiopathologischen Mechanismus einer diffusen beim Bronchialasthma vorkommenden Bronchialobstruktion erlangen konnen

Indem er die neuesten Erkenntnisse der Therapie allergischer Affektionen berucksichtigt und nachdem er feststellte dass wir uns heute in einer stationaren Fortschrittsphase auf diesem Gebiete befinden betont der Autor

Behandlung bei gewissen Fallen einer Ueberempfindlichkeit gegen weibliche Sexuellhormone besprochen hat richtet der Autor seine Aufmerksamkeit auf gewisse physiopathologische Aspekte die sich aus der Anwendung von Cortison ACTH und deren Derivate ergeben indem er ihr Interesse vom Standpunkt der Klinik und Therapie aus aufzeigt

RESUMEN

El autor se refiere a los aspectos mas importantes referentes a los distintos temas tratado en el symposium

En el terreno de las afecciones alergicas examina 1 las reacciones provocadas por medicamentos de frecuencia creciente y cuya clasificación y mecanismo patologico discute 2 las reacciones causadas por insectos y 3 los trastornos psicosomaticos

El autor trata luego brevemente el problema de interes especialmente patogénico de la inmunoquimica de la expectoración del asmatico haciendo notar el interes de estas investigaciones desde el punto de vista del mecanismo fisiopatologico de la obstruccion de los bronquios

Refiriendose a los progreso recientes en la terapeutica y senalando que actualmente se atraviesa un periodo estacionario a ese respecto el autor recalca la importancia adquirida por los tratamientos con hormonas Discute la acción sobre los trastornos hormonales la possibilidad de una terapeutica eficaz en algunos casos de hipersensibilidad a hormonas sexuales femeninas y llama la atencion sobre ciertos aspectos fisiopatologicos del empleo del ACTH cortisona y de sus derivados cuyo interés clinico y terápeutico indica

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THERAPEUTICS OF ALLERGIC DISEASES WITH HORMONES (*)

by

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INTRODUCTION

Signs and symptoms of allergy or hypersensitivity may be controlled in part, by the administration of adrenal hormones (1) Other internal secretions have no direct influence on this process Hormones from the adrenal medulla and cortex both affect the allergic response but do so in an entirely different manner Epinephrine reverses the secondary effects on smooth muscle produced by histamine and related substances in the

delay

HORMONAL EFFECTS ON SPECIFIC PHASES OF THE ALLERGIC REACTION

The production penetration or release of extrinsic antigens are not affected by epinephrine or corticoids In the production of auto antibodies however corticoids may play a role in that large quantities may decrease their prodution to some extent Two hormones not of adrenal origin may affect the penetration of antigen into the circulatory system under certain circumstances In the hypothyroid state the presence of a boggy mucous

(*) Acknowledgement The authors are indebted to Professor Toshio Torii for much valuable advice in the preparation of this manuscript

membrane in the upper respiratory passages will foster microbial infection and upon the administration of *thyroid hormone* or *triiodothyronine* striking improvement in secondary bacterial allergies may sometimes be observed In children and postmenopausal women the lack of estrogen may occasionally induce atrophy of the mucous membranes of the upper respiratory tract again leading to bacterial infection and more easy penetration of air borne antigens This may be successfully treated by the administration of *estrogen*

In the *production of antibodies* epinephrine is totally unconcerned Corticoids on the other hand may affect antibody production profoundly in virtue of the fact that they lead to lysis of lymphocytic elements including plasma cells generally implicated in the production of antibodies (2) Lympholysis occurs to a limited extent only at the replacement level (30 ± 10 mg hydrocortisone daily) but may be extreme at doses 5 to 10 times greater Circulating antibodies increase at first but soon begin to fall as the source is gradually wiped out Thyroid hormones counteract the lympholytic effect of corticoids considerably by actually enhancing the build up of lymphoid tissue at the expense of muscle protein (3)

The union of antigen and antibody is in no way, influenced by hormonal action

The response of the target cell to the antigen antibody complex is variably modified The *cell necrosis* is somewhat delayed by large doses of corticoid but this effect is variable and cannot be relied upon *The formation of histamine* is markedly decreased by corticoids (4 5) and there is a marked reduction in the release of this compound into the circulation *Constriction of smooth muscle* induced by histamine is actively counteracted by a direct smooth muscle relaxing effect of epinephrine in organs such as the respiratory system the gut and the bladder Unlike the corticoids epinephrine in no way influences production of histamine and in contrast to antihistaminics it does not block its access to target cells *The cytological response* around the target cells is blocked by corticoids (3) Both epinephrine and corticoids reduce the increased permeability of the vessel wall induced by histamine and related substances The corticoids will reduce the exudation of lymphocytes macrophages and eosinophils into the target cell sites This is done in part by reducing permeability of the blood vessels and in part by inducing a natural lysis of the eosinophilic and lymphocytic element while stimulating the production of neutrophils This overall reduction in exudation is of considerable importance in the anaphylactic reaction where both types of hormone act benefically The general systemic reaction following an allergic upheaval are thus reduced both by epinephrine through its specific actions on smooth muscle and by corticoids in reducing any febrile response and feeling of malaise

It is apparent from this outline that the most effective therapeutic use of adrenal hormones would include both medullary and cortical derivatives It has been well brought out by the experience of many workers that in the treatment of acute bronchial asthma for instance vital capacity may be increased significantly within minutes by epinephrine whereas hydrocortisone derivatives require much longer periods Yet by affecting earlier phenomena in the allergic response corticoids act synergistically with epinephrine and for a much longer period of time

PRACTICAL ANTI ALLERGIC THERAPY

The use of corticotropin

Pure corticotropin or ACTH is a polypeptide Alpha corticotropin from sheep pituitaries which in nature and arrangement is much the same as that of other species contains 39 amino acids Commercial preparations are derived from pig sheep beef and whale pituitaries Most preparations are repository forms intended for subcutaneous or intramuscular administration and labeled as subcutaneous units while lyophilized corticotropins or those in aqueous solution are assayed in terms of intravenous units One intravenous
as much corticotrop
degree of purity co
International units per milligram of dry powder as compared with a potency of 100 ± 20 units per milligram of pure corticotropin which is not commercially available

Corticotropin stimulates the adrenal cortices to enhanced production and secretion of hydrocortisone together with approximately one quarter the amount of corticosterone an equivalent amount of 17 ketosteroids or its precursors estrogens and progesterone derivatives Aldosterone secretion is also increased at least temporarily but falls off significantly with continued corticotropin stimulation Systematic investigation of the responsiveness of the adrenal to corticotropin in varying doses has been carried out by the investigators using a constant intravenous infusion over 8 hour periods in normal subjects The hourly urinary excretion of total 17 hydroxy corticoids was followed and revealed the following fundamental aspects *a*) Less than 1/2 International unit of corticotropin given for 8 hours leads to a submaximal response *b*) More than 1/2 International unit per 8 hours intravenously leads to a maximal steroidogenic response for as long as the infusion lasts and thereafter there is a rapid cessation of secretory activity As the dosage is increased the secretory activity after discontinuing the infusion becomes more prolonged Thus the initial secretory activity of the adrenal cortices are maximal with only little ACTH and the total secretory activity of the adrenal in turn is proportional to the duration of stimulation by pituitary corticotropin which depends not only on the period of stimulation but also on the amount of ACTH the adrenal is exposed to for a given period of time The urinary 17 hydroxycorticoid excretion pattern following maximal corticotropin stimulation may be reproduced by intravenous infusion of hydrocortisone of 10 mg per hour In a normal 70 kg subject this means that approximately 240 mg of hydrocortisone per day represents the maximum secretion of the adrenal cortices With therapeutic requirements greater than 250 mg of hydrocortisone per day corticoids must be employed

In practice long acting corticotropin preparations rather than intravenous administrations are used Of these a 16 p 100 gelatin diluent with 0 5 p 100 phenol is most widely employed Such gel preparations afford a maximal steroidogenic response for varying periods of time depending upon dosage For a twofold increase in the amount of corticotropin a prolongation of increased steroidogenesis of about 1 hour is

produced This calls for giving two injections a day of corticotropin gel whenever large doses are required For example, 160 subcutaneous units given intramuscularly once a day will cause the same steroidogenic response as 20 subcutaneous units intramuscularly every 12 hours There are longer acting preparations used with benefit such as zinc corticotropin and oxycellulose preparations which are useful for prolonged activity with medium sized doses The search for the ideal preparation undergoing minimal destruction in the tissues but producing a sustained slow release of small amounts of corticotropin is continuing

The relative impurity of commercial corticotropin preparation although greatly improved over early ones still leads to an occasional anaphylactic shock only in allergic patients who are suffering from a reduction in adrenal cortical activity This may be found in pituitary insufficiency or in Addison s disease In subjects who have been suppressed by the administration of corticoids for a long period of time and who are then suddenly taken off these corticoids and put on corticotropin exclusively, anaphylactic reactions may rarely be seen In patients with functioning adrenals this is hardly ever observed because corticoids liberated by the action of corticotropin prevent most of the manifestations of hypersensitivity

The clinical effectiveness of corticotropin used in a given patient should be assessed almost exclusively by the therapeutic response There are no base line studies of adrenal cortical function that need be recorded If there is some doubt about the efficacy of the material during therapy one might then either (a) Collect a 24 hour urine over 5 ml of glacial acetic acid and estimate total 17 hydroxycorticoids or 17 ketogenic steroids These should be at least one and one half times the accepted normal range or one should be able to demonstrate a 3 to 5 fold rise in plasma free 17 hydroxycorticoids after the injection of the corticotropin (b) To rely on changes in the eosinophil count prior to and after injection of corticotropin in allergic states is not too reliable since a marked degree of allergy will so increase the production of eosinophils that even fully activated adrenal cortices cannot at times produce enough hydrocortisone to decrease the number of circulating eosinophils

The use of hydrocortisone and related anti allergic corticoids (6 7)

tis

bo

nucleus notably fluorine hydroxyl and methyl groups The first major breakthrough was the production of prednisolone or 1 dehydro hydrocortisone by introducing one double bond in the molecule A 3 4 fold increase in anti allergic activity was obtained without any change in sodium retaining capacity and this meant that sodium retention and edema were largely minimized as undesirable side effects The next improvement consisted of the introduction of a methyl group in the molecule to form methyl prednisolone with a 4 fold anti allergic potency compared to hydrocortisone and ab olutely no sodium retaining potential whatever Approaching this steroid in potency and also with no sodium retaining capacity 16

hydroxy 9 alpha fluoroprednisolone has been evolved which appears to be particularly beneficial against psoriasis in systemic usage To date 2 methyl 9 alpha fluorohydrocortisone has proved to be the corticoid with the highest organic activity being approximately twenty five times as potent in anti allergic or anti inflammatory effects as hydrocortisone However as with many of the potent preparations sodium retention has been increased to three times that of aldosterone which makes it systemically unsuitable

To date the anti inflammatory activity of corticoids have been proportional to their effectiveness as pituitary corticotropin suppressants Based on this method the authors have compared a number of corticoids shown in Table I

TABLE I

Anti allergic corticoids

DRUG	RELATIVE POTENCY	
	Anti allergic	Sodium Retaining
Hydrocortisone	1	1
Cortisone	0 8	1
Prednisone	2 5	0 8
Prednisolone	3 0	0 8
16 Hydroxy 9 Alpha Fluoroprednisolone	3 5	0
6 Methyl Prednisolone	4 0	0
9 Alpha Fluorohydrocortisone	12	>100

The extra adrenal metabolism of corticoids will modify their anti allergic effectiveness Normally the hydrocortisone derivatives are reduced to tetrahydro hydrocortisone conjugated with glucuronic acid and rapidly eliminated in the urine Twenty four hour urinary excretions contain

potency That this does not account for all the enhancement is clearly shown by the fact that the same corticoids have an increased anti allergic effectiveness topically and here there is no question of hepatic inactivation involved Since corticoids have a rather wide distribution sometimes actually over and above the extracellular fluid volume it is not surprising that dosage requirements in general follow surface area and weight Thus children do require lower doses than adults Apart from the intrinsic pharmacological potency varying resistance to inactivation and body weight the state of the patient s glandular balance may also play a role in overall anti allergic potency

In the hyperthyroid state it has been found that the reduction of hydrocortisone and its derivatives is markedly enhanced thereby the levels of circulating free 17 hydroxycorticoids are constantly decreased and this calls forth a secondary activation of the adrenal cortex through pituitary

ACTH secretion As a result daily outputs of 17 hydroxycorticoids may be double that seen in the normal state The converse is true of hypo thyroidism Thus when administering corticoids to hyperthyroids these biological facts must be kept in mind and up to twice the usual dose must be given in order to achieve the necessary therapeutic levels of free and active 17 hydroxycorticoids in the body fluids In the hypothyroid state one should use less than the usual dosage of corticoids

SINGLE DOSE ADDITION OF CORTICOIDS WITHOUT SUPPRESSION OF INTRINSIC ADRENAL CORTICAL ACTIVITY

In rare instances of mild allergic asthma, eczema allergic rhinitis etc the symptomatology might be worse during the early morning hours More often the reverse is true unfortunately However when present at those times one may give a single dose of corticoid equivalent to and not exceeding 30 mg of hydrocortisone by mouth at 8 a m and preferably with breakfast In that event this material with a half life of 2 hours will have disappeared for the most part from the circulation by midnight It has been found that the adrenal cortices work intrinsically much like the charging of a storage battery whereby 70 p 100 of corticoid is excreted from midnight to 9 a m and 30 p 100 from 9 a m to 12 midnight under basal conditions Blood levels vary by a factor of 2 being highest in the early morning hours around 9 a m and lowest around midnight Urinary excretion of 17 hydroxycorticoids follows the same pattern It is because of this concentrated secretory activity from midnight to 9 a m that one is able to add corticoids to the system around 9 a m without seriously impair ing the overall secretory activity of the adrenal cortices If such a one dose substitution therapy fails to lead to clinical results one must then go to the next step

MAINTENANCE THERAPY WITH SUPPRESSION OF ENDOGENOUS CORTICOID PRODUCTION

In this case corticoids are administered around the clock or given as one or two daily injections of long acting repository corticotropin preparations Within a few hours following administration of corticoids changes in the basophils of the pituitary may be demonstrated These cells secrete corticotropin production of which will henceforth be inhibited and lead to adrenal atrophy *Endogenous production of 17 hydroxycorticoids is* completely abolished A reduction in the dosage of corticoids given will be accompanied of necessity by a *fall in blood levels* and a moderate exacer bation of the basic disease Beneficial effects from this type of therapy may be found either in the abolishment of the diurnal variation in adrenal cortical activity or by giving more than the normal daily corticoid secretion which in a 70 kg man amounts to 30 mg $\pm$ 5 of hydrocortisone

DETAILS IN MANAGEMENT

A minimal dose should be aimed at for maintenance therapy (Table II) and nothing is gained by starting with large doses and then rapidly reducing down to smaller levels It is best to start with the equivalent of 30 mg of hydrocortisone or 10 mg of prednisolone in divided doses every 6 hours by mouth and to increase by 10 mg hydrocortisone or 2 5 mg of predni

TABLE II

Practical dose ranges in maintenance therapy

Hydrocortisone	7 5 mg to 15 mg q 6 h p o
Prednisolone	2 5 mg to 5 mg q 6 h p o
Triamcinolone	2 0 mg to 4 mg q 6 h p o
Methyl prednisolone	2 0 mg to 4 mg q 6 h p o
Corticotropin intravenously	20 to 30 I U units in 1 000 ml 5 p 100 D/W I V over 12 hours
Corticotropin Gel	10 to 60 units daily I M in single or two doses
Zinc Corticotropin	20 to 80 units once daily I M

solone every third day adding this increase in dosage at the time of the worst clinical manifestations A control of symptoms of the disease under treatment *of 50 to 70 p 100 should be the aim If this is achieved it may* be kept up over reasonably long periods of continued therapy without producing significant side effects This policy of working from the bottom up rather than from the top down does not hold when one is

esperate conditions so as to minimize antibody production Doses up to 500 mg equivalent of hydrocortisone may be required and have proved life saving in diseases such as pemphigus allergic arteritis or acute anaphylaxis Widespread destruction of plasma cells and lymphocyte occurs while antibody titers are significantly reduced However the side effects will include a marked inhibition of fibroplasia with poor wound healing

EMERGENCY THERAPY IN ACUTE ALLERGY

If one were dealing with a status asthmaticus one would of course first begin *the administration of epinephrine (8) and aminophyllin in order to* dilate the bronchioles and in a few selected circumstances one might want to give antihistaminics so as to block the access of histamine to the target organs At the same time however one would inject 100 to 200 mg of a water soluble hydrocortisone or prednisolone preparations intravenously or intramuscularly *There are two available now the hemisuccinates or* the phosphates Whereas the hemisuccinates are distributed as powders the phosphates are aqueous indred or 50 mg are given 8 hours the next thereafter twice a day *followed by gradual reduction to a maintenance dose if such be* required When shock is present and proves unresponsive to the pressor agents used addition of corticoids will often reestablish blood pressure

SYSTEMIC ANTI ALLERGIC TOPICAL THERAPY

at this time unless one wants to use ointments of the various compounds On the skin 9 alpha fluorohydrocortisone ointments are very effective and so are prednisolone ointments and those made up of some of the newer drugs By and large results will vary with the type of lesion as it allows for penetration of the active corticoid into the affected site Most of the corticoids used will be absorbed into the circulation and if wide areas are covered there will be enough absorption to lead to adrenal cortical suppression through pituitary inhibition

Undesirable side effects in corticoid and corticotropin therapy

As hormones corticoids or corticotropin producing them and other steroids have a multiplicity of action of which the anti allergic effects are only a part The new synthetic derivatives such as methylprednisolone and triamcinolone no longer lead to retention of sodium water and the loss of large amounts of potassium In fact a normal sodium intake is required so as to prevent salt loss and syncope *Any tendency to edema and weight gain* may be prevented by a low sodium diet and potassium could be supplemented in amounts of 1 gram enteric coated potassium tablets three times a day or liquid potassium preparations 15 to 30 mEq t i d with meals Although there may be only minimal or no sodium retention a certain amount of potassium will be continuously lost because of the breakdown of tissue Redistribution of fat and development of a moon face are early changes that can be minimized by diuretics and administration of thyroid hormone especially triiodothyronine 50 to 100 micrograms daily *Hypochloremia hypokalemic alkalosis* is now a rare complication and with it weakness ascending paralysis poor quality heart sounds etc are rarely seen

On the other hand most of the other side effects still persist even

by themselves *Osteoporosis* is a manifestation of a negative nitrogen balance effecting the organic bone matrix It is particularly bad in patients close to and after menopause and can only be partly minimized by anabolic agents and in this case particularly androgens *Striae* of the skin are a direct result of decrease in elastic tissue In growing children on continued corticoid therapy for asthma a nearly complete *arrest of skeletal growth* and maturation has been noted When corticoids are discontinued there is a compensatory growth spurt Thus treating for 8 months to a year with two month periods of corticoid therapy one may approach normal development of height *Glycosuria* is common but often not associated with increased fasting blood sugar levels and thus a renal tubular phenomena Should there be an increase in blood sugar however it is well to search for a family history of diabetes since most of the patients who develop

Table III

Clinically useful anabolic agents

PRÉPARATION	DOSE
A. ANDROGENS	
Testosterone propionate	15 25 mg I M every 2 days
Methyl testosterone (Metrandren)	20-40 mg subling every day
9 fluoro 11 17 hydroxy methyl testosterone (Halotestin)	6 12 mg p o every day
Testosterone cyclopentyl propionate (Depo-testosterone)	100-200 mg I M every 3 weeks
Testosterone enanthate (Delatestryl)	100-200 mg I M every 3 weeks
B ESTROGENS	
Diethylstilbesterol	5 2 mg p o every day
Ethinyl estradiol	5 20 mg p o every day
Water soluble estrogenic preparations (Premarin)	1 25 3 0 mg p o every day
Estradiol valerate (Delestrogen)	10-40 mg I M every 3 weeks
C COMBINATIONS	
Tylosterone (R) each tablet contains stilbesterol 25 mg and methyltestosterone 5 mg	2 4 tab p o every day
Premarin (R) with Methyltestosterone each tablet contains Premarin 1 25 mg and methyltestosterone 10 mg	1 4 tab p o every day
Femandrin (R) each tablet contains ethinyl estradiol 0 02 mg and methyltestosterone 5 mg	2 4 tab p o every day
Deladumone (R) each ml contains testosterone enanthate 90 mg and estradiol valerate 4 mg	1 2 ml I M every 3 weeks

frank diabetes on corticoids have such a history The use of insulin controls the condition Sulfonyl ureas must be worked on more before one can evaluate their place in this type of therapy *Bleeding tendencies* with easy bruisability are seen more common with prednisone and its derivatives than with hydrocortisone type compounds This must again be due to the leakage of smaller vessels produced by partial destruction o muscular elastic tissues and possibly enhanced by circulating heparin like substances A tendency for the development of *thrombophlebitis* and with it coronary occlusions and pulmonary emboli must be anticipated whenever corticoid dosage has been reduced or the drugs have actually been stopped This calls for a very slow reduction in the presence of good hydration and plenty of exercise together with the early institution of anti coagulant therapy when danger signals are noted The mechanism is

ill understood but must be related to increased sludging of the red cells in vessels during and after the reduction of dosage of corticoids *Increased gastric acidity* and gastro intestinal ulcer formation does occur more rarely with the new derivatives It is in part due to increased hydrochloric acid production increased pepsin and probably other factors The use of antacids and anticholenergics when required are most helpful While *nervousness* and *sleeplessness* are always found to some extent which can be overcome by tranquilizers *psychoses* are fortunately rare and call for a gradual reduction of dosage or discontinuance of corticoids if necessary One must always weigh the danger of psychoses against the disadvantages arising from sudden discontinuance A certain amount of *acne hirsutism* and *amenorrhea* is commonly found and can be treated by the usual means *Superinfections* with ordinarily benign organisms occur especially in debilitated patients on very high dosage of corticoids for long periods of time This is particularly true in bronchial asthma with emphysema and a varied flora in the respiratory tract This dreaded complication is minimized by the use of asceptic techniques and antibiotics chosen carefully in terms of the sensitivity of the offending organisms and used only when absolutely necessary so as not to produce resistance *Contraindications* to the use of corticoids have become less rigid Active peptic ulcers acute psychoses congestive failure may be thought of as contraindications However in the latter case the use of methylprednisolone or triamcinolone may actually enhance sodium diuresis water loss and strengthen the activity of cardiac muscle Systemic infections such as milliary tuberculosis fungus infections pyrogenic abcesses etc call for discontinuance of corticoid therapy unless highly effective bacterial agents are used concomitantly

WITHDRAWAL OF THERAPY

In all maintenance therapy corticoids must eventually be withdrawn This is best done by cutting down the dosage very slowly leaving off the night dose first the afternoon dose next the lunch dose last allowing the patient to continue for at least ten days on just a single morning dose This will support the rather inactive pituitary adrenal system at a time when its activity will not be inhibited by extrinsic corticoid administration There is not much to be gained by giving corticotropin in the morning in gel form for a week although this will make the adrenals larger and more responsive One still has to await the final return of pituitary corticotropin On the other hand one should not be mislead by the inevitable corticoid withdrawal syndrome (10) which consists of the return of the disease under treatment in miniature By allowing this to occur and while keeping up small dosages of corticoid in the early morning hours this condition will soon improve One should not hastily reestablish the full maintenance dosage of corticoid Although responsiveness of the adrenals returns to normal after three to five days of corticotropin therapy even though suppressive corticoid may have been given for one or two years the pituitary ACTH mechanism does not resume normal activity for weeks and occasionally months Thus if severe stress occurs within six months after discontinuance of corticoid and/or corticotropin therapy the patient must be given 100 200 mg of hydrocortisone or its equivalent intramuscularly or

intravenously and supported with exogenous corticoid in the event of an overwhelming stress so as to prevent serious corticoid insufficiency and collapse All patients on maintenance therapy should carry a card to that effect

CONCLUSION

The rational use of corticotropin and adrenal corticoids in the management of allergic states calls for the use of epinephrine as well as antihistaminics as heretofore and supplementation of such therapy by corticoids This conclusion is based on the analysis of the specific loci of activity of these various preparations Only the combined therapy offers the maximal benefit Corticoids have proved lifesaving in the maintenance therapy of many allergic conditions but there still remains the unsolved problem of some of the concomitant side effects that have not been eliminated even by the latest modifications of hydrocortisone principally those concerned with their catabolic action The problem for the immediate future remains the search for an agent which will be anti inflammatory and anti allergic without sharing the full catabolic action of hydrocortisone and its derivatives It is entirely possible that such an agent will be found and it would not necessarily have to be a steroid

SUMMARY

The mode of action of adrenal hormones and their synthetic derivatives in the allergic reaction are discussed separately for epinephrine and the antiallergic corticoids The indirect effects of thyroid and estrogens on mucous membranes and the metabolism of corticoids are mentioned The use of various preparations of corticotropin is sketched including intravenous infusions corticotropin gel and zinc corticotropin The various derivatives of hydrocortisone are considered as to their enhanced anti allergic potency and relative absence of sodium retention One dose corticoid therapy maintenance therapy and mesenchymal suppressive therapy are illustrated in relation to the intrinsic activity of the adrenal cortices and as to their clinical indications The inherent undesirable side effects together with the measures used to counteract them are illustrated for both older and newer corticoid derivatives Special attention is paid to methods for minimizing the flareup of allergic disease upon discontinuing corticoid therapy

RÉSUMÉ

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[illegible] ...e part pour l adre-

Il fait mention des effets indirects de la thyroide et des œstrogenes sur les muqueuses et aussi sur le metabolisme des corticoides

L emploi des preparations a base de corticotrophine est brievement décrit

a savoir l infusion intraveineuse le gel de corticotrophine les preparations zinc corticotrophine

Les divers dérives de l hydrocortisone sont etudies en fonction de leur pouvoir anti allergique éleve et l absence relative de proprietes réten tionnelles sodiques

Les differents modes de traitement par l hydrocortisone sont etudies traitement par dose unique traitement d entretien traitement suppressif mesenchymateux en relation avec l activite intrinseque du cortex surrenal et sous *l angle de leurs indications cliniques*

Sont etudiés pour les dérives corticoides plus anciens et nouveaux les effets secondaires indésirables que leur usage implique ainsi que les mesures propres a les combattre

Les méthodes susceptibles d attenuer les rechutes violentes et subites des maladies en cas de cessation du traitement par les corticoides font l objet d une etude particulierement attentive

ZUSAMMENFASSUNG

Die Aktionsweise von Nevennierenhomonen und ihrer synthetischen Derivate in den allergischen Reaktionen wird fur Epinephrin und den anti allergischen Corticoiden getrennt diskutiert Die indirekten Einflusse des Thyreoidhormons und der ostrogenen Substanzen auf die Schleimhaute und dem Corticoidstoffwechsel werden erwahnt Die Verwendung verschie dener Praparationen des Cortisotropins inklusive der intravenosen Infu sionen von Corticotropin Gel und von Zink Corticotropin wird skiziert Die zahlreichen Hydrocortisonderivate werden bezuglich ihrer gesteiger ten anti allergischen Wirksamkeit und dem relativen Fehlen einer Natrium Retention berucksichtigt Die Corticoid Dosierungstherapie die Unterhalt therapie und die das Mesenchym unterdruckende Therapie werden erlau

chen Besondere Aufmerksamkeit wird den Methoden gewidmet die ein Wiederaufflackern der allergischen Krankheit bei Unterbrechung der Corti coid Therapie moglichst minimal halten sollen

RESUMEN

Los autores discuten separadamente el modo de acción de la adrenalina y de los corticoides antialergicos sobre la reacción alérgica Mencionan los efectos indirectos de la tiroide y los estrógenos sobre las mucosas y el meta bolismo de los corticoides Se refieren luego al uso de diversas preparaciones de corticotropina incluyendo su Zinc derivado y la forma de gel Asimismo se considera la potencia antialergica y la relativa ausencia de retención de sodio presentada por los diversos derivados de la hidrocortisona

Los tratamientos mediante una sola dosis de corticoide la terapeutica de mantenimiento y la de supresion mesenquimatosa se estudian clinicamente en

relación con la actividad intrínseca de la corteza suprarrenal Se describen los efectos secundarios producidos por los corticoides y la manera de contrarrestarlos y en particular se indican los metodos para reducir al mínimo los casos de peoría de las enfermedades alergicas producidos al interrumpir el tratamiento

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THE MECHANISM OF DRUG REACTION

by

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Allergic reactions induced by chemicals are not unpredictable but an integral part of the pharmacological potential of drugs

In recent years we have gained information and insight into the action of drugs which act on enzyme systems (1 2 3) Much of the evidence has been derived from studies of the effect of drugs on microorganisms Quastel and Wooldridge (4) showed as early as 1928 that malonate inhibits succinic dehydrogenase Since then many examples of competitive inhibition of enzymes by competing substrates have become known The action of antibiotics on bacterial enzyme systems is still under scrutiny it has been proposed for instance that penicillin might block the dephosphorylation of mononucleotides by alkaline phosphotase prevent linkage between guanine and ribose 5 phosphate or inhibit nucleosidase and nucleoside phosphorylase (5) Chlortetracycline prevents oxygen consumption in the mitochondrial enzyme systems of susceptible microorganisms —interestingly enough this effect is reversible (*in vitro*) by the addition of magnesium ions (6) a phenomenon which might indicate that this antibiotic acts by chelation upon the metallic prosthetic group of the bacterial enzyme

Principles which apply to the effect of drugs on bacterial enzyme systems might apply equally to the enzyme system of mammalian cells Studies of mitochondrial enzyme systems of liver and brain for instance demonstrated that narcotics e g barbiturates prevent the synthesis of adenosine triphosphate (and thus presumably the synthesis of bound acetylcholine) by preventing the coupling of phosphorylation and oxidation (7) It ought to be emphasized however that the demonstration *in vitro* that a drug is capable of inhibiting certain enzyme systems does not imply that this effect must necessarily be responsible for the pharmacological action *in vivo* of the drug

A drug in order to act must be absorbed i e cross boundaries of membrane and vascular bed reach (unbound or bound) the target tissue exert its effect be removed from the site of action and finally be destroyed or excreted

It is obvious that an ideal drug would be a drug that is absorbed from the

gastrointestinal tract without alteration of its molecule which exerts one specific action on one enzyme system which is released after its effect is completed and eliminated without degradation through existing channels of excretion Drugs of such type are known but are in the minority (*) Many drugs are altered during penetration of the lipoid membrane which separates the intestinal tract from the blood stream or the lipoid barrier which protects the cells of the target tissue Most drugs are metabolized —some drugs in fact require biotransformation in order to become active Some drugs yield metabolites of comparable activity some drugs are capable of forming more than one metabolite Brodie and Hogben for instance emphasize the existence of two metabolic pathways for the bio transformation of phenylbutazone *a*) the addition of a phenolic hydroxyl group which does not alter antirheumatic activity but does increase sodium retention and *b*) introduction of an alcohol group in the butyl side chain which abolishes antirheumatic effect but initiates uricosuric action which is absent in the parent compound Some drugs (like phenylbutazone) are stored in plasma some are stored in fat (e g fat soluble thiopentone or dibenamine) Some like the acridines are stored in parenchymatous tissues Excretion might require further modification of structure or conjugation which accomplishes solubility and allows passage through excretory membranes the formation of glucuronides for instance is used to facilitate the excretion of salicylates

It is probably fair to state that the enzymatic potential of the body will be applied to the handling of any new chemical which challenges it Drug reactions with which we are concerned will develop through unexpected and undesirable interaction of drug and enzyme The drug might *a*) inactivate an enzyme system which is essential in physiological regulations e g cholinesterase, which is inhibited by a great variety of compounds of varied structures *b*) act as a structural analogue of an essential enzyme and thus act as an antimetabolite as do sulfonamides and folic acid anta gonists *c*) be handled through innocuous channels in the majority of individuals but cause symptoms in those in whom these normal channels are deficient or absent viz primaquin induced hemolytic anemia and *d*) undergo partial degradation but in the absence of appropriate enzyme sys tems or systems of conjugation resist complete metabolic breakdown and subsequently combine with suitable tissue components to form antigenic conjugates in other words act as a hapten

a) The first of these possibilities—the interference with the inactivation of an enzyme system which participates in normal physiological regula tions—illustrates the complexity of the problem Drugs which inhibit a single enzyme system are rare 2 acetyl amino 1 3 4 thiadiazole 5 sulfo namide (Diamox) is an example of a compound which acts selectively upon renal carbonic anhydrase *b*) Some chemicals however can act as substrates for multiple enzyme systems e g acetaldehyde (depending on tissue sites) can be eliminated by aldehyde oxidase aldehyde dehydrogenase glyceraldehyde 3 phosphate dehydrogenase carbolygase or aldolase (9)

(*) Brodie and Hogben recently published extensive studies on the conditions under which solubility pH dissociation constants and concentration influence absorption of drugs from stomach and small intestine

enzymes which are inhibited by tetra ethylthiuram disulfide which causes accumulation of acetaldehyde after alcohol intake

Enzymes on the other hand e g pseudocholinesterase an acetyl cholinesterase—may be inhibited by a variety of apparently unrelated substances

Studies on the acetylcholine acetylcholinesterase system which we have carried out during the past five years indicate that there are in blood and tissues significant variations in the titer of the enzyme which might be specific for the biochemical makeup of the individual Williams (10) who studied values of various enzymes in the plasma of eleven healthy young persons under basal conditions at weekly intervals found that ten out of eleven showed a variety of abnormal findings e g of alkaline phosphatase cholinesterase and others and that only one out of eleven maintained his biochemical profile consistently within a normal range Obviously then drug reactions which are based on the inhibition of acetylcholinesterase might occur if the pretreatment titer of the enzyme is already depressed Morphine for instance which inhibits cholinesterase might be tolerated by one patient without untoward effects but cause death of the next patient by the uncontrolled action of acetylcholine on bronchial asthma We have made similar observations on patients who develop severe respiratory symptoms or symptoms of urticaria after administration of acetylsalicylic acid The evidence which we have gathered from more than four hundred patients of this type suggests that acetylsalicylic acid inhibits cholinesterase (*) Pre treatment depression of cholinesterase will enhance reactions to acetylsalicylic acid in one instance a patient developed symptoms of intolerance to acetylsalicylic acid under prostigmine therapy but was able to tolerate significant amounts of the drug after prostigmine was withdrawn

b) The second possibility—the administration of a competitive substrate for existing enzymes—has been one of the major approaches to the development of new drugs Woods (12) demonstrated in 1940 that the bacteriostatic action of sulfonamides was due to selective replacement of paraamino benzoic acid a substance essential for the growth of bacteria In rapid succession the same principles—the competitive inhibition of enzymes which are needed for the utilization of growth factors—were applied to pteroylglutamic acid and to purine analogues which inhibit the synthesis of

( ) Reactions to acetylsalicylic acid a e limited to certa n tis ues particularly the mucous membrane of the respiratory tract Th y are made poss ble *a*) by its ineffective deacetylation of the compound in the blood stream and *b*) by its ab l ty to penetrate the hypothetic l membrane *b*) wh ch s part of the acetylchol ne choli nesterase system at the level of the motor end plate Acetylcholine apparently is held at the motor end plate as a l poprotein complex Activat on of the chemical mediator depolarizes the membrane permits passage of depolarizing substances and initiates the breakdown of the active chemical into its inactive components chol ne and acetate During the resting period re synthesis and re attachment of the re synthesized mediator to its l poprotein moiety occurs Experiments are in progress to localize the part of the cycle at which acetyl sal cylic acid exerts its effect

normal tissue an enzyme which consequently can be blocked without untoward effects on normal growth In this second group it is often difficult to distinguish between contemplated result and untoward reactions since the latter is often an exacerbation of the former

c) The third alternative—a deficiency in enzymes which are present in the majority of the members of a species—is apparently rather common Patients who develop hemolytic anemia after exposure to primaquine or pamaquine are now known to be deficient in a cellular enzyme glucose 6 phosphate dehydrogenase which protects non susceptible individuals (13) Similarly inherited deficiency in pseudocholinesterase produces a prolonged response to succinylcholine (14) Alcohol and barbiturates cause intermittent exacerbation of porphyria (15) Hereditary hyperbilirubinemia is due to the lack of enzymes which conjugate bilirubin with glucorinides (16) Examples of other gene mediated enzyme deficiencies are numerous and include alcaptonuria and ochronosis phenylpyruvic oligophrenia and many others Some of these diseases might reflect the total absence of a specific enzyme One might suspect that many diseases and reactions are caused by relative rather than by absolute deficiencies of one or more enzymes which are essential for the maintenance of normal biochemical reactions

d) The fourth possibility—the partial degradation of drugs which are transformed into haptens—is of more immediate concern to us than the three preceding mechanisms of drug reactions because the deficient enzymatic potential leads to the formation of antigens and to sensitization It is certain that the body is equipped to eliminate drugs in various ways e g by oxidation reduction and enzymatic transformation It is likely that a sequence of biochemical prodecures will be applied until the drug or the fraction of the drug assumes a molecular configuration which will not permit either further breakdown or as it were elimination Paraphenylene diamine for instance is a common source of sensitization It does not sensitize however as paraphenylenediamine but as the molecule to which it has been reduced quinone diimine From an evolutionary point of view it is most interesting and rather strange that the human organism is apparently capable of processing after ingestion complicated dyes and alkaloids which occur in nature and that the difficulties which cause drug reactions are essentially difficulties caused by unnatural chemicals If a chemical or—should attempts of effective breakdown fail—fractions of the chemical are capable of combining with tissue components and thus form a hapten the conjugate becomes antigenic and induces the production of antibodies possibly (if a teleological thought might be permitted) in an attempt to neutralize the chemical moiety

Many drugs which can serve as haptens (either by their nature or by the nature of their fractions) have characteristic structures Kracke and Parker (17) suggested the term benzamine for a group of compounds in which an NH_2 group is attached to the benzene ring—a group which includes sulfonamides procaine and para amino salicylic acid Other antigenic [illegible] idine e g thiouracil mesantoin and [illegible] benzamine and a pyrimidine (18) [illegible] to produce sensitization more readily than other drugs it is certain that many other chemicals can become haptens and engender sensitization

The mechanism of antigen antibody reactions caused by drugs is in essence the mechanism of Masugi nephritis the newly formed antigen initiates the production of antibodies which are released and combine with the fixed antigen at the site of the conjugation

Antigens which are formed by conjugation of tissue components and haptens must fulfill the criteria set forth by Burnet as prerequisites for antibody formation Burnet (19) postulates for instance *a*) that antigens must be either proteins or complexes of an antigenic determinant with protein polysaccharide and possibly nucleic acid *b*) that antigenicity varies some antigenic patterns are better antigens than others *c*) that haptens cannot stimulate the formation of antibodies but can react with antibodies after they have been formed *d*) that the antibody response shows genetic variations and variations according to species *e*) that antigens are taken up by macrophages of the endothelial system but that antibodies are formed by cells of the lymphocytic series and *f*) that antibody formation continues after the disappearance of antigen It is apparent that Burnet s set of rules which form the basis for his self marker hypothesis applies to antibody formation induced by drugs and accounts acceptably for the experimental and clinical evidence with which we are familiar

The formation of antibodies—a final step in the biotransformation of drugs—is the initial step in the sequence which leads to drug reactions Nature and localization of these reactions must depend on fortuitous factors which require further study It seems likely that the nature of the antigen determines the site of the antigen antibody reaction The antigen however is a conjugate of a chemical with a tissue component in other words it requires not only the presence of a suitable hapten but also the readiness of the tissue to combine with it Tissues vary in their capacity to react Hay fever represents an example of such variation It is caused as a rule by a mechanism which resembles the mechanism of drug reactions ragweed (a small polypeptide) serves as a hapten which combines with a component of respiratory mucous membrane and renders it antigenic In most instances receptiveness of the respiratory tract for ragweed and similar haptens appears to be inherited—yet we have observed development of hay fever in non allergic persons when injury to or severe inflammation of the respiratory mucous membrane occurred during the height of expo ure and encouraged the formation of hapten tissue conjugates Injury and inflammation are not however the only localizing factors It is possible for instance to produce granulomatous changes in heart and blood vessels of experimental animals by injection of massive doses of hete

bed are likely to develop typical—serum sickness like—lesions Kallos ang Pagel (20) have studied this phenomenon in guinea pigs a species which seems to have a rather protected vascular bed and rarely responds to sensitization with vascular reactions If guinea pigs however were subject to vascular stress e g continuous injection of caffein during the period of sensitization post mortem examination uncovered severe damage to myocardium and to the media of larger vessels Whether similar pacemakers determine the localization of drug reactions for instance of gene

ralized periarteritis is unfortunately still a matter of speculation

In man the interpretation and classification of allergic reactions to drugs is complicated by at least two possible pitfalls First the disease for which the drug was given might still be active and in fact furnish the fortuitous factors and thus determine the type of reaction which we observe Second even drug reactions which are essentially allergic might be modified by effects of the hapten on other enzyme systems—effects which might co exist at the time of the antigen antibody reaction We suspect that para aminosalicylic acid sensitivity represents a model of such dual action The analogues of para aminobenzoic acid produce a variety of antigens and accordingly of antigen antibody reactions It is likely that sulfonamides have a strong affinity for components of the vascular bed and thereby are prone to cause focal or generalized arteritis Unlike acetylsalicylic acid (which lacks the amino group and rarely if ever produces sensitization) para—aminosalicylic acid imitates the type of sensitization induced by sulfonamides In addition however para aminosalicylic acid has a specific effect of its own it can produce virocytes which are indistinguishable form the virocytes of infectious mononucleosis (21) We are tempted into assuming that both the alleged virus of infectious mononucleosis and para aminosalicyclic acid compete for a nutrient which is essential for the proper growth and nutrition of lymphocytes We might be wrong indeed The appearance of virocytes might represent a sensitization phenomenon caused by a virus acting as a hapten by para aminosalicylic acid acting as a hapten—a conclusion supported by reports that virocytes occur in non allergic conditions (22) The answer—whatever the answer—will clarify at least one small section of an investigative area which is bound to become one of the more immediate one of the more promising challenges in allergy because it permits experimental approach and experimental decision

SUMMARY

Intolerance and sensitivity to drugs habe become a major investigative and clinical problem

It is relatively simple to understand allergic responses induced by com plete antigens The mode of action of drugs which are partial antigens on the other hand needs further clarification Our studies in this area include

tors which determine the localization of these reactions

RÉSUMÉ

L intolerance et la sensibilisation aux medicaments sont devenues un des principaux problemes cliniques et un de ceux qui justifient le plus de recher ches

Il est relativement simple de comprendre les reactions allergiques provoquees par les antigenes complets Le mode d action d autres sub tance qui ne sont que partiellement antigeniques demande à etre eclairci

Nos etudes dans ce domaine nous ont amene à nous efforcer de

1 Isoler les composants des tissus qui pourraient se combiner avec une partie des élements chimiques

2 Établir la difference entre l action de la combinaison anticorps antigene et les effets non immunologiques qui pourraient simuler des reactions allergiques par exemple les reactions hémolytiques dues aux dérives de la quinoline chez des sujets presentant une déficience génetique des groupes sulfhydryle

3 Identifier les agents qui determinent la localisation de ces reactions

ZUSAMMENFASSUNG

gene sind benotigt andererseits weitere Klarung Unsere Studien auf diesem Gebiet verfolgen den Zweck (1) Gewebekomponenten zu isolieren die mit dem chemischen Teil sich verbinden konnen (2) Zwischen Folgen der Antikorper Antigen Verbindung und nicht immunologischen Effekten die allergische Reaktionen stimulieren konnen — zu unterscheiden z B hamolytische Reaktionen die bei Patienten mit genetisch bedingtem Mangel an Sulfhydrilgruppen durch Quinolin Derivate hervorgerufen weden Und (3) Faktoren zu identifizieren die die Lokalisation dieser Reaktionen bestimmen

RESUMEN

La intolerancia y la sensibilidad a las drogas constituyen problemas de gran importancia clínica y de investigacion

Asi como es relativamente simple explicar las reacciones alérgicas producidas por antigenos completos las drogas que son antígenos incompletos actuan de una manera todavía no bien aclarada Los autores estudian este problema en tres direcciones 1) tratando de aislar componentes tisulares

plo las reacciones hemolíticas provocadas por los derivados de la quinolina en pacientes con una deficiencia genética de grupos sulfhidrilos y 3) identificando los factores que determinan la localizacion de estas reacciones

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DRUG INDUCED DISORDERS

by

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The phrase drug induced disorders is a label currently applied to a varied group of syndromes noted as having followed the administration of a number of heterologous substances to human beings well otherwise ill or potentially so Equally vague labels as drug reactions and drug allergy although historically correct and useful for practical purposes are also employed to separate from each other parts of the same great group of phenomena

The first word of each of these three labels the word drug refers to a substance defined only on the basis of its purpose This is usually the mitigation or prevention of disease or else relief of associated distress until resolution occurs by recovery or death The last words of each of the phrases namely disorders reactions and allergy refer to states which can not only occur idiopathically but also as part of the natural course of the disease being treated They can also occur concomitantly as caused by otherwise harmless substances as foods inhalants bacterial fungal and viral infections insect stings venoms and physical agents as solar roentgen other types of radiation and trauma

Despite the frequently unproven causal relationship between drug and disorder and because of the many instances in which the substance cannot be re administered or when it has been causes no reaction there are nevertheless a number of syndromes recognized as having been induced by remedial substance

At this point it must be stressed that the picture of drug reactions undergoes continuous change as emphasis shifts A substance useful in rheumatoid arthritis but known to cause leukopenia may be proscribed for the former but become the drug of choice in the latter Reports of such reactions cease to appear in the literature although the drug continues in use An antihistaminic agent rejected in allergic states becomes a sedative An antitubercular drug similarly becomes a psychic energizer Often thereafter because the drug is prescribed in perhaps a higher dose in another

type of patient of a different age group afflicted by an unrelated disorder new types of reactions become apparent to additional investigators

Some of the confusion apparent in the literature might be lessened if drug induced disorders were loosely and temporarily placed into three large groups

The first is that repeated from text to text It places together the reactions noted with drugs available today but used chiefly 20 30 years ago Such reactions do occur but are reported less and less often in the literature

Four of the classic reactions are labelled as (a) toxic effects (b) secondary effects (c) idiosyncrasy and (d) intolerance These occur both in sick patients and normal subjects A fifth the Jarisch Herxheimer reaction is usually seen only in presently infected patients Two more the Shwartzman reaction and the Arthus phenomenon occur in experimental animals but similar phenomena have been observed in humans

Toxic effects if not controlled as are those of digitalis curare and nitrogen mustard are truly poisonous equally affecting all mammals Many so called non toxic drugs can cause death Wallman recently reported (1) a fatality with drowsiness coma respiratory arrest twenty five hours following ingestion of chlorpromazine 350 mg The word toxic is not applied to a drug which exercises such effects on extremely rare occasions

Secondary effects are merely undesirable reactions under the circumstances of present use Examples are the drying of mucous membranes from atropine or somnolence from antihistaminic agents More important are super infection and vitamin deficiency

Idiosyncrasy is a qualitative abnormal response usually paradoxical as when barbiturates cause excitement or antihistaminic agents urticaria These are easily understood on the basis of two facts The greater the variation from normal of the function affected the less the effect With extreme variation there is the opposite effect

Intolerance is an abnormal quantitative reaction seen when small doses of iodides cause sialorrhea quinine cinchonism or acetylsalicylic acid salicylism

The Jarisch Herxheimer reaction is caused by the release of exotoxins or endotoxins from killed bacteria following the over eager use of antibiotic agents in syphilis typhoid fever and brucellosis

Recent work by Weil and Spink (2) has suggested that this type of reaction may in part be anaphylactoid Intravenous injection of dogs with the lipoprotein carbohydrate complex common to gramnegative bacteria and among others of Brucella militensis and Salmonella typhosa causes defecation and vomiting which may both become bloody These are followed by hypotension and hyperpnea with excitement and then coma There is a leukopenia and a decrease in platelet count Histamine like substances appear in the blood of the inferior vena cava But the shock is not due to intoxication of the central nervous system since it is not changed by vagotomy chordotomy or decapitation The reaction differs from anaphylactic shock in that it first causes no changes in blood coagulability and second in that the effect is delayed Anaphylactoid rather than anaphylactic this type of reaction is evidently related to those similarly caused by peptones venoms and extracts of parasites It is seen

in patients suffering from bacteremia due to infection with gramnega tive organisms

The Shwartzman phenomenon occurs in experimental animals when tissue cells have been exposed to a bacterial filtrate given locally Intrave nous injection of the same material causes hemorrhagic necrosis In humans the Shwartzman type of reaction has been reported upon by Nelson and Braslow (3) as occurring in a child who died following penicillin admi nistration

The Arthus phenomenon is a local anaphylactic reaction seen with cells

mally to a remedial substance ordinarily harmless Suddenly in sickness or in health small quantities occasionally infinitesimal cause mucous mem brane edema smooth muscle spasm the serum sickness like syndrome or dermatological reactions as urticaria angio edema morbilliform scarlati niform or polymorphic erythematous rashes or exfoliative dermatitis Nasal stenosis or coryza bronchospasm or urticaria may last usually for days but if perpetuated by other drugs or disorders or physical agents continue to plague the patient for months and rarely years Spontaneous remissions have been noted but also more serious and more extensive reactions to re administration of the same or a related substance Almost all of the so called allergic reactions can also as noted occur spontaneously with exposure to otherwise harmless substances as pollens danders insect stings venoms foods and trauma and as well as due to physical agents as heat

terms may be misleading For example although in many previously reported cases of sensitivity to aminopyrine no antibodies had been disco vered Halpern (4) reported on a patient sensitive to aminopyrine who presented positive skin tests and positive direct and indirect passive transfer tests In a patient who responded to stibophen (Fuadin) with thrombocytopenic purpura a type of reverse passive transfer has also been demonstrated by Rivera et al (5)

The longest known and as yet the most puzzling of all reactions are those termed serum sickness like The original serum sickness syndrome was itself paradoxical Its incidence increased with increase of dose up to 85 per cent for injections of 100 200 ml of serum dropping to 18 20 per cent with larger amounts As is known to all allergists typical patients respond with rash fever adenopathy arthralgia and leukopenia with lym phocytes Studies with radioactive isotopes by Dixon (6) show that part

have been separately named

Any one of the signs or symptoms may occur alone This is also true of the serum sickness like syndrome of drug allergy due not to colloids as for example serum but to crystalloids as for example penicillin These acting perhaps as haptens may cause the appearance of any part of the syndrome in any one patient When all the reacting patients are studied as a group it becomes apparent that between them they present the complete picture of classical serum sickness and with succeeding exposures serum allergy In the former some aspects of the syndrome may be subclinical In the latter especially with anaphylactic shock it may be that the human patient is reacting with the type seen in either the guinea pig or the rabbit or the dog or to any of these and in addition in human fashion with as well urticaria morbilliform rubelliform or scarlatiniform rashes not so far noted in animals

When there is acute emphysema plugged bronchi and normal blood pressure the guinea pig reaction is being experienced The rabbit type is characterized by general shock and the pulmonary signs are absent In the rare canine type there is a fall of blood pressure and decreased blood coagulation time

There is a subgroup of allergic reactions which must be mentioned at this point An impurity unknown at the time may be responsible for widespread reactions ascribed to a medication truly reactive in its own right Anaphylactic responses have been known to follow injection of diphteria pertussis tetanus vaccine It took the ingenuity and perseverence of Rosenblum (7) to note a positive intracutaneous reaction to silk in one such patient and to track down this sensitivity to its true source namely the use of silk screens in the filtration of the vaccines All published reports of reactions to such vaccine must be reevaluated in the light of this new and recently corroborated study

In this subgroup belong the reactions which require two agents as when the substance must be injected simultaneously with smallpox vaccine or the site of an injection must be exposed to solar or roentgen radiation or else as reported by Gutmann (8) whose patient responded with severe urticaria to penicillin administration after having suffered a bee sting In animals mice for example injected with Hemophilus pertussis acquire a decreased tolerance for histamine

In humans this also occurs As noted ten years ago by Dale (9) histamine may be intrinsic or extrinsic In the former the cell both releases histamine and reacts to it In the latter the cell releases histamine which is carried through the body to cause reactions in other cells There is a no man s land where intrinsic histamine affects cells nearby especially those of the vascular system The damage noted is then of two types in that other local cells are affected not by the histamine release but by the vascular damage These three types of histamine damage may be caused by drugs which release histamine Among others must be listed atropine quinine neoarsphenamine polymyxin chlortetracycline morphine amphetamine curarine and dextran Of the drugs listed one dextran according to Langdell et al (10) may prolong bleeding time This may make it difficult to classify a reaction due to its use If the drug is again administered before histamine repletion has occurred no reaction takes place

But here again there is overlapping and similarity of effects due to drugs

the state of the patient and to exposure to normally occuring substances not used in the treatment of disease Among such histamine releasing substances are those present in the tentacles of the medusa and sea anemone cowhage (from which is derived itching 'powder) amino acids as arginine and lysine and their derivatives carnosine and ornithine and as well lymphagogues naturally present in lobster and mussels (See Halpern B N (11) also Halpern and Briot (12) and Halpern Musso and Neveu (13) and an excellent review by W D M Paton (14)

Some of these drugs and naturally occuring substances act qualitatively on all species but some on single enemy species Some also cause the release of heparin and Slow Reacting Substance Only some of the effects are therefore abolished by antihisminic agents These may act either to compete with histamine at effector cell levels or else by reducing the permeability of vascular cells or again by other pharmacological effects They cannot therefore in these cases be used a diagnostic tool In other words in treatment their failure to relieve does not prove the reaction to be non allergic.

We may eventually be forced to distinguish between a patient allergic to lobster and one whose tissues are rich in histamine released by the ingestion of lobster The amount of histamine present and its type may determine the patient s susceptibility or freedom from reaction on successive exposures The picture becomes more complex with the realization that not only does it take time for histamine repletion to occur but the heparin simultaneously released may react with the histamine releasing substance preventing further histamine release

The administration of a drug as for exemple morphine can conceivably cause the release of large amounts of histamine and thereby be followed by an allergic reaction although morphine is not a true allergen And since in no antigen antibody reactions so far studied has a histamine liberating substance been discovered the question of drug induced disorders of the allergic type due to known histamine releasing medications becomes more

are conversely actually lowered The sensitized guinea pig uterine horn made non reactive to histamine will nevertheless contract when challenged by an antigen The uteri of rats and mice relaxed by histamine contract anaphylactically Histamine induced gastric acidity and ulceration are not affected by the administration of antihistaminic drugs Observely it takes the injection of relatively large amounts of histamine to reproduce allergic phenomena If as Geiger (16) has suggested the anaphylacic response of the ileum of the guinea pig is related to stimulation of the post ganglionic nerve fibers then the protection afforded by substances as diverse as botulinum toxin nupercaine, urethane and aliphatic alcohols exonerates both histamine and acetylcholine as causative agents

We can steer clear of the complex mechanisms of reaction involved and yet mention that other substances may be important Ingenious experiments

by Waalkes et al (17) have shown that by pre treating the rabbit with reserpine plasma serotonin levels do not rise while histamine plasma levels do although both usually increase in the plasma during anaphylactic shock The plasma does not therefore mirror the cell levels of a suspected substance and cannot be used as an indicator of its possible effects There is increasing evidence that serotonin increase at the cellular leve may be an important factor but it is too soon to be certain at least until much currently completed work is published and corroborated

No discussion of this subject as it refers to drugs and patients would be complete unless brief mention were made of two additional sources of symptoms often ascribed to drugs So called normal subjects who volunteer their services or are paid for assistance in the evaluation of drugs are not in any sense of the word normal Safeguards must be set up to prove that the drug is taken The reactions described must be viewed with great scepticism Secondly sick patients are not normal In double blind tests the placebos given have been demonstrated as causing every major allergic response including rashes urticaria and other reactions ascribed by the physician to the toxic effects of the drug in some cases sufficient to lead to its dis use In addition placebo effects perhaps psychogenically induced include dizziness the effects of hyperventilation dyspnea bronchospasm precordial pain diarrhea constipation diuresis anesthesias parasthesias and actually syncope The literature on such reactions using a potent drug a placebo and psychotherapy is vast In one such by Fischer and Dlin (18) the effects of the drug and the placebo could not be distinguished from the number of patients improved Those however given psychotherapy alone showed the greatest improvement

The third great group of reactions to drugs began to be noted about thirty years ago with the introduction among others of the modern anti malarial antimicrobial anticonvulsant antihypertensive antihistaminic antiarthritic antithyroid antibiotic agents as well as the sulfonamides arsenicals the systemic analgesics the smooth muscle relaxants the tranquilizing agents the vitamins and the cortical hormones Measured in amounts prescribed the antibiotic agents now top the list with the tranquilizing drugs being second

Becoming more prevalent during the last ten years new types of drug induced disorders have been increasingly noted Some merit special mention They are the (*a*) histaminic (*b*) genetic (*c*) collagenic (*d*) rheumatic

the reaction may occur alone repetition is necessary for purposes of classification

Polymyxin chlortetracycline amphetamine and dextran among other drugs cause histamine release In hyperhistaminemic patients they may induce histaminic effects not seen when as noted a second administration occurs before body cell histamine repletion has taken place

Genetic effects are allergic in nature but require no sensitizing incubation period as with hemolysis affecting Negroes given primaquine diphosphate (Primaquine) The atopic subject may have inherited a tendency to become allergic although there is some doubt that for the general population this

hypothesis may be true But in the Negroes susceptible to Primaquine effects the specific type of allergy is inherited and previous exposures incubation periods and sensitizing doses are not a part of the response

The collagen diseases among which must be included systemic lupus erythematosus polyarteritis and thrombotic thrombocytopenic purpura have in themselves become a major study represented by texts devoted to them alone (19) For lupus physical chemical and bacteriological agents especially streptococci as well as drugs vaccines and sera have been incriminated Sulfonamides penicillin hexamethonium chloride and hydralazine hydrochloride have apparently caused lupus with the last reproducing the lesion in animals In some of the patients the rheumatoid arthritis syndrome may develop into the lupus erythematosus complex These patients also become photosensitive Some react as well with pericardial and synovial effusions which subside with cessation of the use of the drug and recur with re administration

For polyarteritis the evidence is stronger that the disorder is a type of hypersensitivity caused by drugs and among others sulfonamides penicillin streptomycin neomycin diphenylhydantoin sodium (Dilantin) thiourea phenylbutazone para aminosalicylate acid and steroid hormones Bronchial asthma has beed noted in the histories of 12 .5 per cent of the patients Hypertension has also been seen more frequently than would be expected

According to Large (20) there is a group of patients in whose pulmonary vessels are seen stages of vasculitis ranging from acute fibronoid necrosis to healed fibrosed lesions with discrete nodular granulomas characterized by radially arranged epithelioid and giant type cells

The fifteen patients described by Churg and Strauss (21) all presented severe bronchial asthma fever eosinophilia and evidence of vascular insufficiency of a number of organs According to Allen (22) allergic granulomatous arteritis has followed the administration of sulfonamides or sera

In the thrombocytopenic patients the disorder was preceded in many cases by both upper respiratory tract infections and as well the use of drugs so that the etiological factor might just as well have been bacterial

Selective hemotoxic effects are beyond doubt known to follow use of a number of drugs especially aminopyrine allyliso propylacetyl urea (Sedormid) and phenylbutazone Strong suspicion exists that antergan tripelenamine hydrochloride (Pyribenzamine) acetanilid antithyroid and antibiotic drugs may be etiologic agents A recent report by Callahan and Burrell (23) incriminates methampyrone (Dipyrone) chlorpromazine and the hydantoin derivative Mesantoin Four of the five patients had laryngitis and the fifth *inflammation after a tooth extraction* Three died during the first episode of agranulocytosis

But the total over all incidence of blood dyscrasias has not markedly increased during the last three decades excepting in proportion to the population It has been estimated that 1 500 000 lives have been saved because of antimicrobial drugs especially the sulfonamides and penicillin If the mortality rate from pneumonia had continued as of 1937 then between 1938 and 195. there would have been more than 1 000 000 deaths from this one infection Puerperal sepsis would have killed 76 000 mothers 136 000

syphilitics would have died and a mere 90 000 patients from peritonitis following appendectomy But these patients lived some of them to suffer other disorders of which a proportion were due to drug administration Some, of course developed blood dyscrasias The numbers who might have died are subtracted from the statistics of the deaths from the initial disorders treated but added to the morbidity and mortality of a new set of disorders and diseases in as much as the total percentages must add up to one hundred and eventually every patient dies It is for this reason among others that a true evaluation of the situation is difficult A patient who would have died of infection because of his agammaglobulinemia now lives because of both antibiotic agents and globulin It is for these, among other reasons that all antibiotic agents have headed the list as supposedly hemo toxic substances In many cases the use of the antibiotic drug was unwar ranted

A number of household substances as furniture polish and industrial solvents as benzol may cause blood dyscrasias and lastly the infections and disorders treated with these drugs are (and were known to be) themselves associated with dyscrasias as recorded by the older hematologists long before the new drugs were introduced A patient with a hypoplastic bone marrow

Experimental data from studies on animals cannot be applied to man In the rat succinylsulfathiazole causes agranulocytosis and anemia not by a direct hemotoxic effect but because it inhibits the intestinal bacteria which synthesize *in the rat folic acid Human beings do not* depend on such synthesizing organisms for folic acid and for them the drug is not hemotoxic by this mechanism

The hemotoxic effects of drugs have been explored in detail by Reznikoff and Wells (24)

An interesting subgourp is represented by the patients who suffer from megaloblastic anemia which appears some years after major surgery of the stomach

Lower nephron nephrosis has been observed following the use of a number of drugs but consistently with trimethadione and paramethadione (Tridione and Paradione) as well as with incompatible blood and following the now discredited treatment of staus asthmaticus with intravenous sucrose solu tions

Neurotoxic reactions can be general as Parkinsonism caused by chlorpro mazine (Thorazine) which can also lead to convulsions The reaction may be specific as is the vestibular dysfunction local peripheral neuritis and distant parasthesias associated with injection of streptomycin and the deafness following the administration of Dihydrostreptomycin sulfate Sensitivity to one may not necessarily occur with sensitivity to the other Epileptiform seizures and Parkinsonism may be caused by reserpine

Hepatotoxic reactions may be due to chlorpromazine (Thorazine) thiou racil and methimazole (Tapazole) which thicken bile or by direct action on liver cells as caused by dinitrophenol and trinitrophenol Among the newer drugs causing similar hepatotoxic effects are the anticonvulsant agent

phenylacetyl urea (Phenurone) the antiarthritic agent phenylbutazone and the antitubercular drug isonicotinic acid hydrazide

Among the drug effects of the lung mention must be made of hexamethonium which directly causes an acute fatal interstitial pulmonary fibrosis Falk and Newcomber have also reported on Loeffler s syndrome following penicillin administration (25)

Cardiac disorders due to drugs range from the well known arrhythmias caused by digitalis to the ventricular tachycardia induced by quinidine Less often reported are the tachycardia and ventricular fibrillation following procaine amide (Pronestyl) administration and the premature ventricular contractions due to Rauwolfia preparations Stibophen (Fuadin) and sulfa

causative bacteria are resistant He may falsely conclude that greater amounts of the responsible agents should be prescribed Mention of such effects has been made but repeated at this point for purposes of classification and emphasis

Physicians occasionally like to regard their patients from another point of view and that is on the basis not of causes but of effects The dermatological reactions easily lend themselves to such classification

In the skin pruritus has been reported following the administration of acetylsalicylic acid aminopyrine antibiotic agents atropine codeine emetine the mercurials the opium derivatives phenobarbital and the sulfonamides

Acneiform furunculoid and erysipelas like eruptions may be due to the use of adrenocorticotrophic hormone bromides chloral hydrate iodides oils and tars

Eczematous eruptions can be caused by local anesthetic drugs antibiotic agents arsphenamine atabrine chloral hydrate ephedrine formalin the mercurials procaine and quinine

Erythema multiforme like responses habe been noted in patients sensitive to acetophenetidin antibiotic agents antipyrine the barbiturates the iodides phenolphthalein the salicylates and the sulfonamides

The bromides iodides salicylates and sulfonamides may cause erythema nodosum like eruptions

Fixed eruptions have followed ingestion of acetophenetidin antipyrine arsphenamine Atabrine atropine acridine bismuth cinchophen emetin mercury phenacetin salicylates and sulfonamides and injection of gold salts

Purpuric eruptions have been seen to follow the administration of arsphenamine the barbiturates the carbamides ephedrine guanidine the iodides the mercurials the salicylates the sulfonamides and thiouracil

The drugs which may cause contact dermatitis are too numerous to list

If we wish to consider oxygen as a drug then its administration at high levels to premature infants interferes with proper metabolism of the sulfhydryl group of respiratory enzymes leading among other things to retrolental fibroplasia This too must then be termed a drug induced disorder

The disorders caused by antibiotic agents may be allergic or non allergic in type They have been adequately reviewed by Rentchnick (26) and

Schindel (27) Briefly it can be said that there is no known allergic disorder that they cannot induce or mimic

Allergists are equally familiar with the many manifestations of steroid administration or withdrawal

This brief review does not discuss more than one per cent of the subjec of drug induced disorders The problem faced by any reviewer is not what to include but what to omit

We are living during times when it is more important than it ever was for the physician to know every aspect of the clinical manifestations of the disorder being treated Allowing for the natural variation of patients from each other any deviation from the natural classical course of recovery or else concurrent appearance of any other type of disorder however classical should lead the physician to suspect the therapeutic agents used

ilar effects

ave been at

follow up

studies for months and sometimes for years should be part of the patient s therapeutic program

Atopic individuals appear to be prone to drug reactions and in them the least allergenic drugs should be prescribed and to them the closest obser vation given

Every patient reactive or non reactive should have available a list of drugs ingested applied or injected so that future reactions can either be avoided or else ascribed to the true causative agent Only by some such method can the great number of drug induced disorders be diminished and the patients present and future welfare safeguarded

SUMMARY

The classic reactions to drugs include (a) the toxic effects as seen with controlled doses of curare (b) secondary effects as vitamin deficiencies follo wing antibiotic medication (c) idiosyncrasy as when barbiturates cause exci tement and antihistaminic agents result in urticaria (d) intolerance as iodism

appar

repor

tion

the site as the initial injection

The typical allergic reactions previously known as atopic' are characte rized by mucous membrane edema smooth muscle spasm the serumsick ness like syndrome urticaria angio edema and various dermatidites

During the last decade eleven new types of reactions are with increasing frequency being reported

A number of drugs as polymyxin are now known to be histamine relea sing in type These in hyperhistaminic patients cause the so called hista

mimic reaction. There is a genetic type of sensitivity as seen in Negroes given Primaquine In these no previous exposure or sensitization period is necessary The three types of collagen diseases namely systemic lupus erythematosus polyarteritis nodosa and thrombotic thrombocytopenic purpura have apparently followed the use of hexamethonium hydralazine dilantin thiourea phenylbutazone and antibiotic agents

Selective hemotoxic effects are beyond doubt known to follow aminopyrine phenylbutazone antergan tripelennamine hydrochloride acetanilid antithyroid and antibiotic agents

Lower nephron nephrosis has consistently followed the use of trimethadione and paramethadione Neurotoxic reactions can be caused by chlorpromazine in general and in particular by streptomycin and dihydostreptomycin as well as by reserpine

Hepatotoxic reactions may be caused by Thorazine thiouracil and methimazole and rarely isonicotinic acid hydrazide Fuadin and sulfadiazine may causa a myocarditis while cardiac function may be changed by quinidine

any deviation from the natural classical course of recovery or else the concurrent appearance of any other type of disorder however classical should lead the physician to suspect the therapeutic agent used Every patient should have available a list of drugs used so that future reactions can be avoided or ascribed to the true causative substances

RÉSUMÉ

Les reactions classiques aux medicaments comprennent

a) Les effets toxiques comme ceux observes pour des doses controlees du curare

b) Les effets secondaires comme les avitaminoses apres l administration d antibiotiques

c) Les idiosyncrasies dans les cas par exemple ou les barbituriques provoquent un etat d excitation et les substances antihistaminiques de l urticaire

d) Des phenomenes d intolerance comme l iodisme et le quinisme qui apparaissent a la suite de l administration de ces medicaments a des doses inferieures a la normale

La réaction de Jarish Herxheimer se produit parfois apres un usage excessif d agents anti microbiens qui liberant de grandes quantités de toxines bacteriennes semblent aggraver l etat du malade

On signale l apparition du phenomene de Schwartzman chez un enfant mort a la suite d une administration de penicilline et aussi l apparition d un phenomene d Arthus lorsque les injections d un medicament sont répetees a l endroit meme de la premiere injection

Les reactions typiquement allergiques et connues autrefois sous le nom d « atopiques sont caracterisees par l œdeme des muqueuses le spasme des muscles lisses un syndrome semblable a la maladie du sérum l urticaire l œdeme angio neurotique et les dermites diverses

Durant la derniere décade on a signale onze nouveaux types de reactions medicamenteuses dont la frequence va en augmentant

Le pouvoir libérateur d histamine de nombreuses substances comme la polymixine est connu Ces substances provoquent ce que l on nomme reactions histaminiques

Il existe un type genetique de sensibilisation observee chez les noirs traites a la primaquine Ces reactions se manifestent sans qu une exposition préalable ou une période de sensibilisation soient necessaires

L apparition des trois types de maladies du collagene le lupus erythemateux generalise le purpura thrombocytopenique et la polyarterite noueuse a ete observee apres traitement par *l hexamethonium l hydralazine* la *dilantine la thio uree* la *phenylbutazone* et les *substances antibiotiques*

On sait de façon certaine que des effets hemotoxiques selectifs suivent parfois l administration d aminopyrine de phenylbutazone d antergan de tripelenamine d acetanilide de substances antithyroidiennes et d antibiotiques

On a observe et on a impute des nephroses a l emploi de la *trimethadione* et de la *paramethadione*

Des reactions neurotoxiques peuvent etre dues à la chlorpromazine et plus particulierement a la streptomycine la *dihydrostreptomycine* et aussi a la *reserpine*

La *thorazine* la *thio uracil* le *methimazole* et plus rarement l *hydrazide de l acide iso nicotinique* peuvent provoquer des phenomenes hépatotoxiques

La fuadine et la sulfadiazine peuvent causer des myocardites alors que la quinidine l amide procainique et les preparations a base de rauwolfia peuvent amener des troubles de la fonction cardiaque

De nombreux medicaments ont un effet pyretogene Compte tenu des differences de temperaments existant entre les malades toute anomalie dans le processus normal de guerison ou l apparition de troubles si classiques soient ils doivent amener le medecin a suspecter l action possible des substances administrées Chaque malade devrait disposer d une liste des remedes qui lui furent administres pour pouvoir reconnaitre ses reactions ainsi que les medicaments qui sont contre indiques

ZUSAMMENFASSUNG

Klassische durch Medikamente hervogerufene Reaktionen

a) Toxische Wirkungen wie sie durch kontrollierte Dosen von Curare hervorgerufen werden

b) Sekundare Wirkungen wie Vitaminmangel nach Verabreichung von Antibiotici

c) Idiosynkrasie in denjenigen Fallen in denen zum Beispiel Barbiturate eine Exzitation und Antihistaminsubstanzen eine Urticaria hervorufen

d) Intoleranz Phanomen z B gegen Jod und Chinin das sogar bei unter normalen Dosen auftritt

Die Jarish Herxheimer Reaktion tritt bisweilen nach exzessivem Gebrauch von antibakteriell wirksamen Substanzen auf die durch Freisetzen grosser Bakterientoxinmengen den Zustand des Kranken zu verschlimmern scheinen

Man berichtet uber das Auftreten einer Schwartzmann Reaktion bei einem infolge von Penicillin Applikation verstorbenen Kind sowie uber die Erscheinung des Arthus Phanomen wenn man an der Ursinjektionsstelle weitere Injektionen von Medikamenten fogen lasst

Die typischen allergischen und bisweilen als atopisch bekannten Reaktionen sind charakterisiert durch ein membranoses Odem Spasmen der glatten Muskulatur ein *Syndrom ahnlich der Serumkrankheit Urticaria neu*rotisches Angio-Odem und verschiedene Dermatitiden

[illegible]

eine Exposition oder Sensibilisierungsperiode vorhergehen muss

Die 3 Typen der Bindegewebserkrankungen der Lupus erythematodes generalisatus die Purpura thrombocytopenica und die Polyarteritis nodo a scheinen nach Behandlung mit folgenden Substanzen aufzutreten *Hexamethonium Hydralazine Dalantine Thiourea Phenylbutazon* und *antibiotische Substanzen*

Man weiss sicher dass selektif hamotoxische Wirkungen nach der Gabe von Aminopyrin, Phenylbutazon Anterganchlorhydrate Tripelennamin Acetanilid und anti thyreoiden und antibiotischen Substanzen zu Tage treten

Man beschrieb Nephrosen die nach der Verwendung von Trimethadion und Paramethadion auftraten und damit in Zusammenhang gebracht wurden

Neurotoxische Reak*tionen konnen allgemein durch* Chlorpromazin besonders durch Streptomyzin *Dihydrostreptomyzin* und auch durch das Reserpin hervorgerufen werden

Thorazin Thiouracil Methimazol und seltener Isonicotinsaurehydrazid konnen hepatotoxische Erscheinungen provozieren

Fuadin und Sulfadiazin konnen Myocarditiden verursachen Auch konnen Chinidin Procainamid und Rauwolfia Praparate Herzfunktions storungen herbeifuhren

Viele Medikamente erzeugen Fieber Berucksichtigt man die Konstitutionsunterschiede der Kranken so sollen alle Anomalien des normalen Heilungsvorganges oder das Auftreten von klassischen Storungen besonders den Arzt an die mogliche Wirkung verabreichter Substanzen denken lassen Jeder Kranke sollte eine Liste der ihm verabreichten Medikamente haben, um im folgenden seine Reaktionen auf eventuell verursachende Medikamente zuruckfuhren und die bei *ihm kontra indizierten Medika*mente erkennen zu konnen

RESUMEN

Las reacciones clásicas a las drogas incluyen (a) la accion toxica como la provocada por el curare (b) efectos ecundarios como la deficiencia vitaminica que aparece luego de las medicaciones antibioticas (c) fenomenos de idiosincrasia como la excitación causada por los barbituricos o la urticaria por los

antihistamínicos (d) fenómenos de intolerancia como los provocados por dosis mínimas en el iodismo o cinconismo

La reaccion de Jarisch Herxheimer se observa como consecuencia del uso abusivo de antibióticos que conducen a la liberacion de grandes cantidades de toxinas bacterianas la reacción de Shawrtzman ha sido indicada en el caso de un niño que fallecio como consecuencia de una inyeccion de penicilina y el fenomeno de Arthus cuando se efectuan varias inyecciones de una droga en el mismo sitio

Las características de las reacciones alérgicas típicas llamadas anteriormente «atopicas» son edema de las mucosas espasmo de la musculatura lisa síndrome tipo enfermedad del suero urticaria edema angioneurotico y varias dermatides Durante la ultima decada han sido senalados once nuevos tipos de reacciones con incidencia creciente

Algunas drogas como la polimixina se han demostrado ser histaminoliberadoras y provocan la llamada reaccion «histaminica» en algunos pacientes Hay un tipo de sensibilidad que se observa en los negros que reciben primaquina para el que no es necesaria una exposicion previa Los tres tipos de enfermedades del colágeno lupus eritematoso poliarteritis nodosa y purpura trombocitopenica han sido producidos aparentemente como consecuencia del uso de hexametonium hidralazina Dilantin tiourea fenilbutazona y agentes antibioticos

No hay duda que la aminopirina fenilbutazona Antergan clorhidrato de tripelenamina acetanilida y agentes antibióticos pueden producir efectos hemotóxicos El uso de trimetadiona y parametadiona ha provocado consistentemente nefrosis Clorpromazina estreptomicina dihidroestreptomicina y reserpina han sido la causa de reacciones neurotóxicas Thorazina tiouracilo metimazol y mas raramente la hidrazida del acido nicotínico pueden provocar efectos hepatotóxicos La Fuadina y la sulfadiazina pueden provocar miocarditis y la funcion cardiaca puede ser alterada por la quinidina procaina y preparaciones de Rauwolfia

Muchas drogas tienen accion piretica

Sin dejar de tener en cuenta las diferencias entre un paciente y otro cualquier desviacion del curso normal de mejoria o la aparicion de nuevos tipos de desórdenes deben hacer sospechar la accion del agente terapeutico usado Cada paciente debería poseer una lista de las drogas que ha recibido de manera de poder evitar futuras reacciones

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A PROPOS DES SYNDROMES CLINIQUES ET DU MÉCANISME DE L'ALLERGIE MÉDICAMENTEUSE

par

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A la suite des exposes « up to date » presentés par MM Brown et Samter nous nous bornerons ici à quelques remarques generales concernant d une part la prevention des accidents d allergie medicamenteuse d autre part le role de la posologie et des sensibilisations de groupe dans la genese de ces accidents

En ce qui concerne la *prevention* nous ne nous etendrons pas sur le fait aujourd hui *souligné de toutes parts que tout médicament aussi inoffensif* qu il paraisse en substance est un poison en puissance et qu il n en existe aucun qu il s agisse de produits anti infectieux diurétiques anti névral giques ou tranquillisants qui ne puisse devenir responsable de la mort non seulement d un ou plusieurs malades mais aussi de sujets bien portants Aux divers *mécanismes agressifs aujourd hui élucides il s en ajoutera* certainement de nouveaux et divers auteurs suisses (Zollinger Moeschlin Gsell Miescher) ont recemment démontre que la phénacétine considerée par de nombreux pharmacologues comme l un des plus anodins parmi les calmants de la douleur était en realite responsable par l action irritante qu elle exerce sournoisement sur les reins d un nombre impressionnant

[illegible]

de la therapeutique de plus en plus indispensable

Abstraction faite de la stricte observation des *indications thérapeutiques,* on dispose aujourd hui en vue de prévenir les accidents d allergie médi camenteuse de deux mesures principales d une part l adjonction d un antihistaminique de synthese aux produits connus pour l exceptionnelle frequence de leurs effets allergisants d autre part l administration con jointement aux *médicaments dont l emploi parait indispensable chez des* sujets qu on sait sensibilisés à leurs effets d une dose appropriée d A. C T H ou d un dérivé de la cortisone

En plus de ces mesures protectrices il nous a paru avantageux, pour

eviter ou retarder l apparition des processus de sensibilisation en general de preferer toutes les fois que cela parait possible la *voie d administration digestive* aux voies d administration parenterales On sait que Richet lors qu il decrivit il y a soixante ans le choc anaphylactique expérimental fut vivement intrigue par le fait que ce phenomene ne se produisait que lorsque la sensibilisation etait réalisee par voie parenterale tandis que l ingestion des proteines étrangeres responsables de l anaphylaxie ne provoquait meme aux doses les plus massives ni la sensibilisation de l animal ni le declenchement du choc chez l animal sensibilise Il en conclut que la mu queuse intestinale constituait une barriere protectrice soit parce qu elle provoquait l inactivation des protéines sensibilisantes soit parce qu elle etait infranchissable a leur fraction anaphylactisante

Ce probleme dont Richet ne put apporter la solution definitive fut ultérieurement repris par son fils qui demontra avec la collaboration de Guy Laroche et de Saint Girons au cours d une serie de recherches sur l allergie alimentaire que la sensibilisation par voie d ingestion etudiee avec le blanc d œuf et le lait n etait nullement irrealisable mais qu elle exigeait des quantites d antigene plusieurs centaines de fois plus elevées que celles agissant par voie parentérale Cette importante constatation trop longtemps tombee dans l oubli doit etre retenue par les thérapeutes C est pour cette raison que la phenoxypénicilline administree par voie orale aux doses de 400 000 a plusieurs millions d unites par jour ne pro voque que tres rarement la sensibilisation des malades Aussi merite t elle du fait de son extraordinaire innocuite de se substituer aux injections parenterales en vue du traitement de la presque totalite des etats infectieux penicillino sensibles Elle constitue pour la meme raison la medication prophylactique de choix des infections streptococciques Il importe toutefois de savoir que la penicilline utilisee par voie orale si son action sensibi lisatrice est pratiquement insignifiante est néanmoins susceptible de declen cher des complications allergiques ou meme des accidents anaphylactiques severes chez les sujets sensibilises par son administration parenterale anterieure Ce n est la d ailleurs qu un motif de plus a l administration de la penicilline par voie orale



On s e t essentiellement occupe jusqu ici lors de l etude du mecanisme de l allergie medicamenteuse du role d ailleurs primordial de la cons titution chimique des médicaments Apres avoir appris grace aux travaux de Landsteiner que non seulement les proteines mais aussi certains corps possédant la structure physio chimique des cristalloides étaient doues de proprietés allergisantes on s efforça de discerner dans la formule complexe de nos medicaments modernes le radical chimique responsable de l al lergie La connaissance de ce radical généralement inactif par lui meme etait essentielle a l etude des composants humoraux et tissulaires suscep tibles en se combinant avec les antigenes incomplets de leur conférer leurs propriétes allergisantes Elle etait non moins indispensable à l iden tification des divers territoires dans lesquels s effectue le choc de l anti

gene et de l anticorps de meme qu a l etude des facteurs susceptibles de déterminer cette localisation

En opposition avec le role primordial accorde a la constitution chimique de l allergène on ne s est que peu occupe jusqu ici de la *posologie* la plus apte a sensibiliser les malades Diverses observations nous ont toutefois démontre que ce facteur ne devait pas etre sous estime en pratique S il est certain que la posologie *declenchante* ne presente qu une importance mineure les accidents allergiques pouvant etre provoques par des quantites infimes du produit auquel le malade s est sensibilisé il nous parait non moins evident que les doses élevees *sensibilisent* plus facilement que les petites doses

Nos premieres observations dans ce domaine datent de 1945 époque a laquelle nous avons pu nous persuader a l occasion de nos premiers essais de traitement des thyréotoxicoses par les antithyroidiens de synthese que les accidents d agranulocytose — manifestation allergique la plus couramment observée avec ces produits — etaient notablement moins frequents avec le *methyl thiouracil* qu avec les autres dérives de la thiourée Cette plus grande innocuite du methyl thiouracil tient apparemment au fait que ce médicament deploie sa pleine efficacité a doses relativement faibles ne dépassant dans la regle pas 250 mg par jour et que ces petites doses sont vraisemblablement beaucoup moins aptes a jouer le role actif d antigene que les quantites plus fortes necessaires avec les autres produits Ainsi s explique que les premiers cas d agranulocytose au methyl thiouracil aient ete observés chez des sujets ayant reçu les doses anormalement elevees et certainement inutiles de 800 mg (Pindborg) et 1200 mg (Lundbaeck) de methyl thiouracil par jour C est probablement pour la meme raison qu on a observe une diminution notable de la frequence des agranulocytoses dues au classique thiouracil (Astwood) depuis qu on a abaissé la dose d attaque de ce médicament de 2 g a 1 2 g puis successivement a 800 et meme 600 mg par jour

Les memes constatations se repetent lorsqu on etudie l action sensibili-

une autre specialité renfermant 500 mg d aminopyrine par dose Cette remarquable innocuite d un produit dont on consomme annuellement en Suisse plus d un million de doses ne peut guere s expliquer que par sa faible teneur en pyramidon

Peut etre en est il de meme de la *penicilline* dont les proprietes allergisantes reconnues par les premiers auteurs qui l utiliserent sur une grande échelle furent attribuées tout d abord a diverses impuretés difficilement separables de l antibiotique lui meme De fait la presence des manifestations allergiques cutanees etait appelee a diminuer au fur et a mesure que s accentuait le degre de purification du produit L accalmie ainsi realisee ne fut toutefois que de courte duree les incidents allergiques devant par

la suite augmenter à nouveau de frequence au point de frapper aujourd hui 10 p 100 environ des sujets traites par la penicilline Si cette recrudescence tient avant tout a ce que les sujets recevant l antibiotique de façon prolongee ou en cures repetees sont chaque année plus nombreux il importe peut etre aussi de tenir compte du fait que la posologie aujourd hui appliquee est de dix à cent fois plus élevee que celle considérée comme normale il y a quinze ans lors des premieres applications cliniques de la penicilline

Un second element dont le therapeute ne saurait jamais assez tenir compte est celui de la *frequence grandissante des sensibilisations croisees* en raison desquelles un sujet peut se montrer plus ou moins fortement allergique a un produit qui lui est administre pour la premiere fois La sensibilisation ne constitue en effet pas une reaction spécifique a un medicament donne mais bien une reaction specifique a un antigene determine antigene qui peut etre commun a des medicaments doues non seulement de proprietes biologiques et therapeutiques différentes mais aussi de proprietes chimiques tres diverses

Étudie tout d abord avec les sulfamides le phenomene de sensibilisation croisee se revela fort complexe Alors que certains sujets paraissent demeurer indefiniment sensibles a un seul sulfamide il en est d autres qui apres s etre sensibilises a tel d entre eux par exemple au sulfathiazol se revelent par la suite sensibles a la sulfapyridine et a la sulfadiazine ceci tout en demeurant refractaires a l action allergisante de la sulfanilamide Toutes les combinaisons paraissent possibles dans ce domaine et ce n est que peu a peu que l on est parvenu a preciser les radicaux chimiques qui comme les groupes hydroxyl carbonyl et amino sont les plus aptes a fonctionner comme haptenes

Parmi ces sensibilisations de groupe l une des plus frequemment rencontrees est celle qui s exerce tout a la fois vis a vis des anesthésiques locaux des sulfamides et de *certaines pénicillines depot* dont l effet antibiotique prolongé est dû à l adjonction de procaine Nous avons observé en particulier a plusieurs reprises des reactions anaphylactoides générales chez des sujets qui apres avoir éte traités localement par des poudres sulfamidees ou par des onguents a base de Benzocaine (éthyl aminobenzoate) de Panthesine (diethylleucinol aminobenzoate) ou d un anesthesique local dérive de l acide para aminosalicylique reçurent ulterieurement en raison d une infection dont le peu de gravite ne justifiait pas toujours cette mesure une injection de procaine pénicilline Les sensibilisations croisees les plus imprevues sont susceptibles de se manifester et nous avons assiste recemment a une crise anaphylactique de haute gravité chez un sujet qui atteint de manifestations allergiques séveres a l acide para aminosalicylique (PAS) avait reçu a titre de medication antiallergique une injection intraveineuse de Phenergan Les deux produits bien que presentant a premiere vue une formule de constitution tres differente comportent neanmoins l un et l autre un groupe amino lie a un noyau benzenique Plus recemment encore nous avons observe quelques heures apres la prise initiale de 1 g de Kynex (sulfanilamido methopyridazine) chez un sujet jadis sensibilisé a la sulfadiazine l apparition d un exantheme allergique febrile Ces quelques exemples suffisent a montrer combien le praticien lorsqu il prescrit un medicament nouveau aussi bien que lorsqu il utilise un produit dont les propriétés allergisantes sont connues doit etre constamment sur ses gardes et pret a intervenir

RÉSUMÉ

En présence de l'accroissement incessant des accidents d'origine médicamenteuse auxquels viennent de s'ajouter les néphrites interstitielles de la phénacétine récemment décrites en Suisse il est devenu urgent de mettre un frein à l'usage abusif d'une foule de médicaments anti infectieux antinévralgiques et tranquillisants

Parmi les tentatives visant à prévenir l'effet allergisant des produits dont l'emploi est inévitable il importe de signaler que la sensibilisation aux médicaments synthétiques modernes si elle est essentiellement conditionnée par la présence de certains radicaux chimiques dépend également dans une certaine mesure du mode d'administration du médicament la voie digestive étant d'une façon générale moins allergisante que la voie parentérale

Un autre facteur souvent méconnu est celui de la posologie Alors que la dose déclenchante de la réaction allergique ne présente qu'une importance mineure l'action sensibilisante est d'une façon générale d'autant plus marquée que le médicament est administré à doses plus élevées C'est ainsi que les agranulocytoses de l'aminopyrine et du méthyl thiouracil relativement fréquentes lorsque la posologie quotidienne dépasse 800 mg sont extrêmement rares lorsqu'elle reste inférieure à 300 mg

La notion de sensibilisation de groupe prend d'autre part une importance grandissante du fait que le praticien rencontre de plus en plus fréquemment des sujets allergiques à un produit qui leur est administré pour la première fois La sensibilisation ne constitue pas une réaction spécifique à un médicament donné mais bien une réaction spécifique à un antigène déterminé antigène qui peut être commun à des produits doués non seulement de propriétés biologiques et thérapeutiques différentes mais aussi de propriétés chimiques très diverses Quelques exemples nouveaux sont donnés à l'appui de cette notion.

SUMMARY

In face of the constant increase of drug induced disturbances to which can be added the interstitial nephritis due to phenacetin recently described in Switzerland it has become an urgent matter to put a curb on the undue use made of a number of anti infectious anti nevralgic and sedative remedies

Among the attempts made to prevent the allergenetic effects of unavoidably employed substances one should point out that sensitization to modern synthetic remedies although its essential condition is the presence of certain chemical radicals also depends to a certain extent on their way of administration generally the digestive way proves to be less allergenetic than the parenteral one

cil are relatively common for daily doses above 800 mg and extremely rare for doses remaining under 300 mg

Besides the notion of group sensitization gains a greater importance as the physician more frequently meets with subjects allergic to drugs administe red to them for the first time

Sensitization does not consist of a specific reaction to a certain drug but of a specific response to a determined antigen this antigen may be com mon not only to other substances having different biological and therapeu tical properties but also very different chemical ones

Some new examples are given to support this conception

ZUSAMMENFASSUNG

Wegen der standigen Zunahme von medikamentos bedingten Zwischen fallen zu denen auch die in der Schweiz jungst beschriebene interstitielle Nephritis durch Phenazetin gehort wurde es notwendig die missbrauchli che Verwendung einer Umzahl von antiinfektiosen antineuralgischen und Beruhigungsmedikamenten zu bremsen

Unter den Versuchen einen allergisierenden Effekt von unbedingt not wendigen Produkten zu verhuten ist es wichtig zu erwahnen dass die Sen sibilisierung gegenuber den modernen synthetischen Medikamenten soferne durch die Anwesenheit gewisser chemischer Radikale bedingt auch zu einem gewissen Grade von der Verabreichungsweise des Medikamentes abhangt der digestive Weg ist im allgemeinen weniger allergisierend als der parenterale

Ein anderer wenig bekannter Faktor ist die Posologie (Lehre von den Mengen in denen die Medikamente verabreicht werden) Wenn die auslo sende Dosis fur die allergische Reaktion auch nur von geringer Bedeutung ist so ist die sensibilisierende Wirkung eines Medikamentes im allgemeinen umso starker je grosser die verabreichte Dosis ist Daher sind Agranulozy tosen durch Aminopyrin und Methyl Thiouracil extrem selten bei Tages dosen unter 300 mg wahrend sie recht haufig bei Dosen uber 800 mg taglich auftreten

Andererseits nimmt die Gruppensensibilisierung immer mehr an Bedeu tung zu was dazu fuhrt dass der Praktiker immer haufiger allergische Per

chen Unterschieden sondern auch verschiedener Chemie gemeinsam vorkommen kann Zur Stutze dieser Behauptung werden einige neuere Beispiele angefuhrt

RESUMEN

En vista

cuentes y a

das por la f

al uso abusivo de una cantidad de remedios anti infecciosos antineuralgicos y tranquilizantes

Entre las precauciones destinadas a prevenir el efecto alergizante de productos de uso indispensable conviene señalar que si bien la sensibilización está condicionada esencialmente por la naturaleza química depende también, en cierta medida de la vía de administracion De una manera general la vía digestiva es menos alergizante

Otro factor a menudo descuidado es la posologia En efecto la dosis desencadenante no tiene gran importancia pero en cambio la accion sensibilizante es más marcada cuando la dosis es alta Asi por ejemplo las agranulocitosis producidas por la aminopirina y el metil tiouracil son relativamente frecuentes cuando la dosis diaria sobrepasa los 800 mg pero son sumamente raras con dosis inferiores a 300 mg

El concepto de sensibilizacion de grupo toma una importancia mayor dia a dia debido a que se encuentran con mayor frecuencia casos de sensibilización a productos administrados por la primera vez al paciente Se trata de una reaccion específica no al medicamento sino a un antígeno determinado que puede ser comun a sustancias cuyas propiedades biologicas terapeuticas y aun químicas son diversas El autor cita algunos ejemplos en apoyo de esta concepcion

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INSECT ALLERGY
A COMMON CAUSE OF HAY FEVER AND ASTHMA

by

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We have reason to believe that allergy to insects next to pollen and fungus spores is a common seasonal allergy in temperate climates and perhaps the most important cause of respiratory allergy in subtropical and tropical regions Our belief is based not on the sporadic or occasional effect of insect stings nor on the exposure to scales or hairs from insects in the air Rather it is predicated on the much more continuous and greater exposure to the dust from the soil and vegetation which contains the pulverized material of dead insects Before we present the evidence for this thesis we will briefly refer to some previous allusions to insect allergy

Allergic reactions and anaphylactic shock from insect stings are the phenomena called to mind to the average physician or lay person when one speaks of insect allergy A large part of the literature on insect allergy deals with such reactions It cannot be denied that such allergy is impor tant particularly since fatalities are not uncommon In the United States there occur annually a number of fatal anaphylactic reactions from the stings of various species of bees Indeed such allergies are among the oldest described The oldest of these is a hieroglyphic account on the tomb of King Menes of Egypt which indicates that he died from the sting of a wasp or hornet in 2641 B C (1)

Insects have also been incriminated as the inhalant causes of allergy either in special regions or during special restricted periods of the year or as a result of special or occupational exposure These reports have included allergy to May
the United States apl
locust(8) bedbug(9) b…
sewage filter flies (13) bee (inhalant) (14) and mites (15) Some of these and other articles concern individual case reports Our own work which

we wish to describe here takes the attitude that everybody is exposed to dusts of a variety of insects a large part of the year and that a large proportion of the allergic population suffers from such alle gy Before we can present figures and facts let us first outline the criteria required to incriminate any substance or group of substances as a causative agent in allergy

CRITERIA FOR A SUBSTANCE TO BE CONSIDERED AS A CAUSE OF INHALANT ALLERGY

1 The source of the allergen must be present in the area in sufficient quantity and should be capable of being carried by the wind If possible the actual allergenic substance should be demonstrated to be present in the air in sufficient concentration to be responsible for symptoms
2 Fluctuation in exposure should be compatible with fluctuations in the allergic symptoms
3 The suspected allergen should show whealing skin reactions in a special group of allergic individuals and not in other allergic persons nor in non allergic persons
4 There should be a tendency to skin reaction to other antigens of a related biologic nature
5 Reaginic antibodies should be demonstrable by passive transfer in non allergic subjects and non sensitized sites should not react to same concentrations of antigen as the sensitized site
6 The potentiality of the substance as a cause of clinical allergy should be demonstrable either by the production of symptoms on experimental exposure of mucous membranes (eye nose bronchi) to the allergen or by the production of systemic reactions after injection
7 Systematic injections of the antigen should result in a diminution of the allergic symptoms

Admittedly not all of the above criteria can be always met in every instance particularly when the alleged allergen involves relatively recent experience The following material describes our experiences with insect allergy keeping in mind the above criteria

DO OBSERVATIONS FULFILL CRITERIA?

CRITERION 1 The top soil contains numerous arthropods as well as other forms of animal life (16) Low vegetation and other plants sustain large numbers and varieties of insect forms Of necessity these insects when dead and disintegrated constitute a portion of the dust carried in the atmosphere and inhaled Such dusts are of course virtually impossible to identify morphologically Specific insect antigens in the dust and soil have not been demonstrated thus far immunologically in preliminary trials

CRITERION 2 In the vast majority of patients (323 out of 400) reacting on skin test with insect antigens the symptoms occurred either in summer months or were aggravated during the summer About 85 per cent had

nasal symptoms 40 per cent asthma while a few had atopic dermatitis or conjunctivitis only The seasons varied but could comprise any period including April to November In those allergic also to molds it was not possible to attribute directly any clinical symptoms to insect allergy since either could occur at the same time It could be argued of course that for the same reason one could not ascribe mold allergy any more than insect allergy as a cause in these cases In spite of these difficulties in 43 per cent of the insect reactors with seasonal symptoms the seasonal pattern could not be explained on molds (because they did not react to them) or on pollens (because the pollen season did not cover the season of symptoms) Only another seasonal agent (insects) could complete these seasonal patterns For example a woman having hay fever from April to November reacted to ragweed (August and September) and grass pollen (June and July) Since there were no tree pollen reactions nothing other than insect antigens could explain the early symptoms and since there were no mold reactions only insect antigens could explain the symptoms in the latter part of the season A man having asthma from May to October and reacting to ragweed pollen (August and September) could justifiably be classed as a case of clinical allergy to insects when he gave positive skin tests with the latter A child reacting to house dust and insects but having hay fever only during June July and August could not have his seasonal pattern explained on the house dust sensitivity

It is understandable that the seasonal pattern would become less apparent the warmer the climate At the same time the probabilities are that in sub

Benaim Pinto (17) who found a very high percentage (66 %) of insect reactors in Caracas Venezuela

Further evidence that an air borne allergen may be a cause in seasonal cases in our regions in those who have positive skin reaction to insect dust are as follows Such patients improve in filtered air in very arid climates or on a sea voyage They have less symptoms when there is little wind or dust

CRITERION 3 The vast majority of skin reactions to insect extracts occurred in those who have respiratory allergy Very rarely were reactions obtained in those patients who had urticaria gastrointestinal allergy or no allergic complaints Most of the reactions were wheals obtained on scratch test It is true that some of the crude insect antigens contain a considerable amount of histamine or a histaminelike substance the highest amounts of which were found in cricket However these amounts were not sufficient to produce a false reaction on scratch tests In intradermal testing all the insect extracts can be trusted to be devoid of false reactions at concentrations of 1 100 000 In concentrations of 1 10 000 occasional

false reactions are produced while in 1 1000 concentrations most of the insect extracts will give positive tests

CRITERION 4 The majority of patients who reacted to one species of insect reacted to a number of others (18) Sometimes as in the case of bee sting allergy the reactions were confined to more closely related species The matter of cross reactions is a very complicated one and no attempt will be made to make an analysis of it here

CRITERION 5 In the early stages of our experience we showed that such insect reactors had transferrable antibodies In further work we have attempted to study relationships of insect antigens by cross neutralization with passive transfer At this point it suffices to say that transferrable antibody was demonstrated in every instance in the blood of patients having good reactions on scratch tests with insect antigens

CRITERION 6 We have not subjected our patients to the inhalation or other artificial exposure to insect antigens However during the course of desensitization we have occasionally encountered systemic reactions from the sensitizing dose

CRITERION 7 Since the results of desensitization mainly depend on subjective interpretation it is difficult to evaluate the effects even when one is dealing with an individual antigen (such as grass or ragweed pollen) It is obvious that it becomes increasingly more difficult to evaluate the results when several antigens are used and particularly in that 57 per cent group where the role of insect allergy cannot be separated But up to date we have had a sizable group in whom desensitization has shown to produce effects which give credence to the role these insect antigens play in the causation of allergy Such benefits have been seen in the following groups (1) New patients whose pollen treatment alone could not account for the season of their relief (2) Patients of the same type previously treated by others without insect antigens (3) Patients whose allergy to insects could not be positively established on the basis of their seasonal pattern who were previously treated by us and others without the use of insect antigens

INSECT ANTIGENS CLINICAL CONSIDERATIONS

The selection of insects for the preparation of antigens for testing and therapy was predicated primarily on two considerations the likelihood of exposure to such insect or closely related one and the availability of the raw material Some of the insects could be obtained commercially, but most of them were only procurable through state or Federal agencies such as Department of Agriculture or U S Public Health Service Because of the constant shifting pattern of insects available the testing was not the same on all patients The following insects (or other animal species) were included in our tests silk (pupa and cocoon) ant pupa house fly grasshopper cricket melon fly Mediterranean fruit fly mosquito (Aedes aegypti) mosquito (Culex) aphid mites honey bee (also wasp hornet bumble bee, etc) caddis fly Mayfly oriental fruit fly mushroom fly,

oriental rat flea moth cockroach daphnia cicada earth worm and others

For desensitization we originally used silk pupa extract or Mayfly In the last 3 years we have employed an insect mixture usually consisting of extracts of the following silk pupa ant pupa Daphnia Mayfly and house fly

In some instances we have used different mixtures or the extracts of individual insects Until more conclusive information is obtained from our studies and perhaps those of others on antigenic relationships of insects the choice for testing and treatment will of necessity depend on our general ideas of exposure on the results of the skin tests and the available sources of insects for the preparation of extracts

For clinical work the insect extracts were prepared in the following manner The insects were obtained fresh or live and placed in deep freeze then dried in vacuum oven The small insects were extracted with ether while the large insects were first ground before ether extraction The ether was poured off and the insect material dried Further grinding of the partially defatted material was followed by a second ether extraction The defatted dry powder was then extracted with a glycerine buffered saline solution using the ratio of 5 gms of powder to 100 ml of extracting fluid After mechanically shaking for 24 hours the material was filtered and then run through a Seitz filter This stock solution was used for scratch tests and as a basis for dilution for intradermal testing and treatment Intradermal tests were usually made with 1 100 000 or 1 10 000 (on the
1

tion

IMMUNOLOGICAL FINDINGS

The necessity for studying antigenic relationship between different species of insects is obvious The insects used for this study were chosen on the basis of previously demonstrated whealing skin reactions in man close taxonomic relationship between some forms more distant relationship between others and availability of adequate amounts of material (19) The insects selected were silk pupa (Bombyx mori) cricket (Acheta domestica) German cockroach (Blatella germanicum) Mayfly (Ephemeroptera) and fly (Phormia regina) After defatting the dry powder was extracted with saline in ratio of 1 10 After 24 hours or shaking the extract was *cleared by centrifugation merthiolate added and frozen*

Antiserum was prepared by injecting rabbits with 4 ml of the 1 10 extract in Freund s adjuvant Bleedings were begun at the end of 4 weeks and if indicated a second antigen injection was given at that time Sera of good precipitation titer were pooled from the periodic bleedings

Hemagglutination and hemagglutination inhibition were carried out with the tannic acid technique of Boyden as modified by Stavitsky (20) In performing the inhibition experiment 4 agglutinating doses of the serum were preincubated with graded dilutions of the antigen followed by the addition of coated cells Since the stock extracts of the antigen fre

quently produced spontaneous agglutination or lysis a 1 100 dilution was used for coating the sheep cells When the agglutinating titer of each serum was determined against sheep cells coated with each extract extensive cross reactions were no ed However only with the homologous extract was there a marked inhibition of agglutination On the other hand cross reactions were inhibited by a wide variety of extracts

The triangle plate technique of Jennings and Malone (21) was used in agar diffusion studies Each extract showed more than one band cricket showing 4 and cockroach 6 When two extracts were used in different compartments there was usually an additional light and diffuse arched zone joining the two agar depots Although such a phenomenon is ordinarily regarded as an identity reaction the interpretation here was confused by additional findings Heterologous rabbit antiserum and even normal rabbit serum of adult and twoweek old rabbits gave similar results Although a number of possibilities—such as the presence of isoagglutinins or other natural antibody—present themselves as an explanation of this phenomenon further work needs to be done to explain it

Passive transfer neutralization studies have been made to a limited extent and are now proceeding on a more extensive scale

Fractionation and purification of insect extracts are in progress

SUMMARY

Our experience indicates that disintegrated substance of insects in the soil and vegetation constitutes an antigenic dust producing numerous cases of asthma and hay fever This report is based on approximately 400 cases of respiratory allergy whose symptoms were due entirely or in part to such insect allergy In substantiation of our claims we have complied with the following criteria necessary to incriminate these substances 1 The omni presence of the source has been demonstrated [illegible]

[illegible] produced on injection 6 Desensitization has been accomplished

A large variety of insect extracts have been studied clinically A smaller group was subjected to cross neutralization studies with passive transfer and hemagglutination and gel diffusion studies The findings thus far indicate that there are common antigens in a wide variety of insects as well as specific antigens Further work is proceding particularly along lines of fractionation and purification.

RÉSUMÉ

L experience nous a appris que les debris d insectes se trouvant dans le sol et dans la vegetation forment une poussiere antigenique responsable de nombreux cas d asthme et de « rhume des foins »

Cette etude est basee sur l observation d environ 400 cas d affections aller

giques respiratoires imputables totalement ou partiellement a l allergie par insectes

Pour appuyer ce que nous avançons et pour pouvoir incriminer de façon certaine les poussieres d insectes nous nous sommes impose les regles suivantes

1 La présence des poussieres a eté dans tous les cas reconnue

2 Aux variations d exposition ont correspondu des variations de symptomes

3 Des réactions cutanees urticantes ont ete obtenues chez certains sujets et pas chez d autres

4 La presence d anticorps reaginiques a ete établie

5 Des reactions généralisees ont été obtenues par injections

6 La desensibilisation a eté reali ee

Une grande variété d extraits d insectes a ete etudiee du point de vue clinique Quelques uns de ces extraits ont ete etudiés quant a leurs pro

nombre d insectes et des antigenes particuliers a certaines especes

D autres travaux sont en cours plus particulierement sur les questions de purification et de fractionnement

ZUSAMMENFASSUNG

in der
bilden

Diese Veroffentlichung basiert auf der Beobachtung von ungefahr 400 allergischen Affektionen der Atemwege die ganz oder teilweise einer Allergie gegenuber Insekten zuzuschreiben sind

den Insektenstaub mit
haben wir uns folgende

1 Gegenwart von Staub wurde in allen Fallen bestatigt

2 Veranderungen der Expo ition gingen mit Veranderungen der Symptome einher

3 Urtikarische Cutanreaktionen konnten bei gewissen Personen erzielt werden bei anderen aber nicht

4 Das Vorhendensein von reagierenden Antikorpern wurde festgestellt

5 Systemische Reaktionen konnten durch Injektionen erzielt werden

6 Eine Desensibilisierung konnte verwirklicht werden

Vom klinischen Standpunkt aus wurde eine grosse Varietat von Insektenextrakten studiert Einige dieser Extrakte wurden wiederholt durch eine passive Uebertragung die Beobachtung einer Hamagglutination und eine Diffusion in Gel medium studiert.

Unsere Versuche zeigten dass es bei einer grossen Zahl von Insekten gemeinsame Antigene gibt andererseits aber auch Antigene die spezifisch fur bestimmte Arten sind

Weitere Arbeiten werden derzeit ausgefuhrt die sich eingehend mit Fragen einer Reinherstellung und Fraktionierung befassen

RESUMEN

Nuestra experiencia indica que los restos de insectos forman un polvo alergenico responsable de numerosos casos de asma y fiebre de heno El presente estudio se basa en aproximadamente 400 casos de alergia respiratoria debidos enteramente o en parte a este tipo de alergeno Nuestras conclusiones se basan en los siguientes hechos 1 La presencia del alergeno ha sido comprobada en todos los casos 2 La exposicion al alergeno está directamente vinculada con las fluctuaciones de los sintomas 3 En algunos casos se han podido obtener reacciones cutaneas 4 Se ha podido demostrar la presencia de reaginas 5 Por inyección del alergeno se han provocado reacciones constitucionales y 6 Se ha podido llevar a cabo la desensibilizacion

Una gran variedad de los extractos de insectos haa sido estudiada clinicamente y con algunos extractos se han efectuado ensayos de neutralización cruzada en pruebas de transferencia pasiva y de difusión en gel Los resultados parecen indicar que hay un antígeno comun a una gran variedad de insectos y ademas antigenos particulares de cada especie Actualmente se continuan realizando trabajos especialmente sobre la purificación y fraccionamiento de estos alergenos

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RESPIRATORY ALLERGY TO INSECTS OF THE ORDER OF TRICHOPTERA

by

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Respiratory symptoms due to allergic sensitivity to various species of insects have been reported in the past many of such instances being of quite local character Such a special situation exists at the head of the Niagara River where it forms the outlet of Lake Erie in the United States In this area insects of the order of Trichoptera (Caddis Flies) are extremely abundant during the summer Because the Cities of Buffalo New York and Fort Erie Ontario Canada are situated along the borders of the Niagara River a large human population is exposed to these insects and allergic individuals not infrequently become sensitive to them

The Trichoptera are aquatic insects all of their life cycle except the adult stage is spent in the water They frequent flowing streams having a

mouth organs After pupation and metamorphosis the adult fly rises to the surface and takes to wing Both sexes fly ashore where mating takes place in the adjacent foliage The female flies back to the water and lays her eggs the male dies ashore

ound in the foliage and in

flies form dense swarms extending two or three kilometers along the shore and up to a kilometer inland At such times the flies may be as thick in the air as snow flakes in a winter storm

The adult flies do not bite Their wings are covered with microscopic hairs which are easily dislodged On the land the dead flies become dessicated and powdered The hairs and powdered bodies float in the air and it is these particles which when inhaled induce allergic sensitivity and cause respiratory symptoms in sensitized persons These emanations are entirely innocuous to normal persons even on intense exposure

The respiratory symptoms produced in persons allergic to the flies are similar to those of hay fever nasal obstruction sneezing and rhinorrhoea

conjunctival irritation and lachrymation cough and bronchial asthma. The nasal and eye symptoms are often marked and the asthma is often very severe

The flies do not wander far from the water and the hairs are not airborne more than eight or ten kilometers from the River For this reason a person sensitive to these flies can secure almost complete relief from their symptoms by going inland ten or twelve kilometers

Direct skin tests with an extract of the whole fly yield immediate wheal type reactions in persons allergic to the Trichoptera Specific skin sensitizing antibodies (reagins) are demonstrable in the sensitive patient s blood serum by the Prausnitz Kustner method Positive conjunctival and nasal tests are obtained with both wing hairs and body particles Typical respiratory symptoms can be induced at any time by the deliberate inhalation of the dried emanations

Treatment by successive injections of increasing doses of an extract of the whole fly yields satisfactory results comparable to similar treatment with pollen extracts in hay fever patients

I have so treated fifty seven patients sensitive to the Trichoptera In ten of these patients the insects were the primary or major cause of their allergic symptoms In the remaining 47 patients these insects were a contributing cause of symptoms

An interesting observation in my experience is the fact that an appreciable number of patients sensitive to the Trichoptera also yield positive skin tests to two other orders of insects namely to the Lepidoptera (butterflies and moths) and to the Ephemerida (May flies)

Another puzzling observation is that certain allergic patients yield positive skin tests to the Trichoptera although they live in regions where they are not exposed to these insects so far as is known but are exposed to the Lepidoptera

Whether these skin reactions noted in these two observations indicate the existence in a patient of separate specific sensitivities to the three different orders of insects or are evidence of an antigenic relationship between the three orders is a matter which requires further study

SUMMARY

Respiratory symptoms due to allergic sensitivity to insects is rather uncommon For this reason it has seemed of interest to report the local occurence of allergic sensitivity to flies of the order of Trichoptera in the region of the Niagara River

Because of the location of two cities on the river a large human population is exposed to their emanations and cases of allergic sensitivity to them are not infrequent.

A description of the insect and of its habits is presented The symptoms and treatment are outlined and the possible relationship between sensitivity to the Trichoptera and to certain other orders of insects is discussed

RÉSUMÉ

Il est rare de constater des cas d allergie due a la sensibilisation aux insectes. Pour cette raison il a semblé digne d intéret de signaler l apparition locale de cas de sensibilisation a des insectes du genre des Trichopteres

Niagara

Des poils microscopiques détachés de leurs ailes et des particules desséchees de leurs corps flottent dans l air a l instar des pollens et peuvent etre inhalés

Du fait de l existence de deux grandes villes baties au bord de cette riviere il se trouve qu une population importante est exposée a ces poussieres organiques et que des cas de sensibilisation a leurs allergenes ne sont pas exceptionnels

Une description de l insecte et de ses mœurs est faite Les symptomes et le mode de traitement sont indiqués et les relations possibles entre la sensibilisation due aux Trichopteres et celles dues a certaines autres especes d insectes sont discutees

ZUSAMMENFASSUNG

Symptome der Atemwege die durch eine allergische Ueberempfindlichkeit Insekten gegenuber bedingt sind sind ziemlich ungewohnlich Aus diesem Grunde schien es von Interesse uber ein lokales Auftreten einer allergischen Ueberempfindlichkeit Fliegen der Trichoptera Art gegenuber in der Gegend des Niagara Flusses zu berichten

Diese Insekten entwickeln sich im Wasser Wahrend des Sommers sind sie im geflugelten reproduzierenden Stadium in extrem reichlicher Menge entlang der Ufer des Niagara Flusses vorzufinden Mikroskopisch kleine Harchen ihrer Flugel und getrocknete Partikelchen ihrer toten Korper schweben wie Pollen in der Luft und konnen so eingeatmet werden Da zwei Stadte an dem Fluss liegen ist eine zahlreiche Bevolkerung diesen Einflussen ausgesetzt und Falle einer allergischen Ueberempfindlichkeit ihnen gegenuber sind nicht selten

Es wird eine Beschreibung dieses Insektes und seiner Gewohnheiten gegeben Die Symptome und die Behandlung wird skiziert und die moglichen Aehnlichkeiten dieser Ueberempfindlichkeit den Trichopteren gegenuber mit der anderen Insektenarten gegenuber werden diskutiert

RESUMEN

Los trastornos respiratorios provocados por alergia a insectos son bastante poco frecuentes Por esta razón el autor ha creido de interes señalar la incidencia local de manifestaciones provocadas por moscas del orden Trichoptera en la región del rio Niágara.

Estos insectos se reproducen en el agua y son sumamente abundantes en verano En esa epoca el aire contiene a la manera del polen pelos micros cópicos provenientes de las alas y partículas de los cuerpos muertos de los insectos Dado que hay dos ciudades sobre el río existe una importante poblacion expuesta a estos factores alergenicos y los casos de sensibilidad a ellos no son raros

Se presenta una descripción del insecto y de sus hábitos Se describen los síntomas provocados y el tratamiento y se discute la posible relación entre la sensibilidad a insectos del orden Trichoptera y de otros órdenes

SPUTUM IN ASTHMA CHEMICAL AND IMMUNOLOGIC CONSIDERATIONS (*)

by

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Bronchial asthma is a syndrome or symptom complex characterized by paroxysms of dyspnea and wheezy breathing of variable duration and infrequently terminating in fatalities during the attack Although a great many etiological factors contribute to the triggering of the attacks of bronchial asthma and one cannot look upon the syndrome as a single disease entity there is a strong possibility that the cellular physiologic and biochemical abnormalities of the paroxysm are common to all bronchial asthma One such abnormality is the subject of the present communication the mucus which accumulates intrabronchially almost exclusively in cases of intrinsic bronchial asthma The asthmatic syndrome is divisible essentially into an extrinsic form in which identifiable and environmental factors either inhaled ingested or injected may provoke attacks of bronchospasm and edema of the bronchial mucous membranes while the intrinsic variety is characterized by these phenomena in addition to the accumulation of large amounts of viscid mucus which may plug the major portions of the respiratory bronchioles throughout both lungs In part our conception of the existence of a form of asthma produced almost entirely by bronchospasm in contract to a form marked by intrabronchial plugging with mucus results from our experience with the many many experiments performed with guinea pigs The classical anaphylactic phenomena which have formed so useful a tool in the investigation of the phenomena of hypersensitivity as it occurs in the guinea pig is essentially an extraordinary degree of bronchospasm and edema of the submucous tissues of the bronchi

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overdose of pollen or mold or the ingestion of a simple chemical compound

( ) Supported by Grant N H 1752 of the United States Public Health Service

like aspirin to which the patient may be sensitive, occurs so rapidly that the physiological disturbance is surely one of bronchospasm and edema such as that which occurs in the guinea pig and a few post mortem studies support this view It is highly probable however that prolonged asthma in the human even when a recognizable extrinsic factor is operative and we do not have sufficient data to establish what prolongation of time is required may be associated with intrabronchial accummulation of a thick mucus which complicates the bronchospasm and edema of the vascular tissues An exquisite example of this was manifested by a nine year old female admitted to St Louis Children s Hospital in a state of extreme asthma occurring within an hour following the injection of a very large amount of penicillin to which she subsequently proved sensitive The penicillin had been administered by her pediatrician as a part of his management of an existing attack of asthma probably however, provoked by ragweed pol len sensitivity Twenty four hours after the first injection of penicillin and about ten hours following a second given at the time of admission she exhibited marked mediastinal and subcutaneous emphysema and was so critically ill that the chest service felt it necessary to perform a tracheostomy and mediastinotomy At the time of the performance of the tracheostomy a moderate amount of characteristically thick viscid acellular homogeneous mucus as aspirated from the trachea and on examination contained very many eosinophiles The child although desperately ill for several days subsequently went on to make a slow but uneventful recovery On several later occasions during the course of skin testing and hyposensitization therapy with weed pollens and mixed air borne molds she developed brief episodes of asthma immediately following the injection of the allergen lending incontrovertible support to the diagnosis of extrinsic asthma This case is briefly reported simply to indicate that even a completely extrinsic asthmatic syndrome may within a very short time of its onset be complicated by the presence of thick intrabronchial mucus

The major portion of this report will deal with the chemistry of this mucus but always in relation to the abnormal physiology of the respiratory tract which may be responsible for and in turn affected by the mucus accummula tion Many experimental studies in the past have explored the relationship between mucus production and such phenomena of the respiratory tract as ciliary activity such studies have been nicely reviewed by Gordonoff in his treatise on the physiology and pharmacology of the expectoration process His own experiments and those of others reveal that the intra bronchial accummulation of the stringy mucus almost always was followed by a decline in ciliary activity and his monograph suggests that the reverse is also true i e that the slowing up of ciliary activity may in itself frequen tly be followed by the intrabronchial accummulation of mucus Both phenomena that is

1 The secretion of mucus and
2 The performance of ciliary activity

are related to other physiological paremeters also reviewed by Gordonoff such as

3 The resorption capacity of the alveoli and lung tissue and
4 The digestion of secretions which accumulate in the lung

A certain number of experiments have already been performed on

these physiological phenomena as well as on the motor phenomena which are concerned with the total expiratory and expectorant process in the lungs There is still considerable controversy regarding many of these physiological processes however because of criticism concerning the quantitative techniques which were used in the various measurements made Nevertechniques which were used in the various measurements made Nevertheless Gordonoff concluded his concept of the physiological expectoration process after his very careful and extensive analysis of all of the physiological experimental work which had preceded the publication of his monograph in the following way

The viscous scanty secretion due to secreting activity of the mucous membrane glands is first of all diluted and liquified The secretion which becomes fluid is in part resorbed The part which is not easily eliminated can be made resorbable through the digestive capacity of the lung parenchyma. The solid particles which still are present migrate by means of the kinetic energy of the respiratory air from the alveoli to the bronchioles to the smaller bronchi and finally to the largest bronchi from where they are either coughed up or migrate out by means of the cilia. Every morning since the breathing becomes stronger after arising large secretion clumps migrate upwards without a cough stimulation where they are either swalled or spit up or coughed out. With older people the respiratory activity is not as strong and because of this there occurs the tendency toward bronchitis

Thus in Gordonoff's review and in his summary of the expectoration process the disposition of the viscous mucus plays an important part in his physiological conceptions His conception still makes good sense despite which there has been very little done and in fact, Gordonoff himself goes into no detail at all regarding what must be a fundamental key to an understanding of the entire process—the chemistry of the mucus itself and its relation to normal and diseased states

The composition of sputum results not alone from mucus production by various glands which line the tracheo bronchial tree but also by contributions from

1 Other epithelial cells lining the respiratory tract

2 Infection and end products of bacterial metabolism and their injurious effect on cells and

3 The end results of the allergic inflammatory stimulus resulting in the appearance of excessive amount of the chemical substance or substances and cellular elements typical of such inflammation.

Thus in this conception the sputum is not regarded as a pure epithelial secretion of a single cell entity but a composite material the most important element of which however may be the mucus

In addition there are surely special genetic influences which predispose certain human subjects to the development of intrinsic asthma. These genetic influences may be reflected in production of abnormal secretion by any of the cellular elements involved or development of abnormal cellular physiologic mechanisms involving enzyme systems which may be concerned with the disposition of respiratory mucus under normal circumstances

In any case it is quite in order to begin someplace in the attack and it

was felt that certain rewarding data might result from initial chemical analysis of the whole sputum before applying the refinements of physico chemical and immunochemical techniques which will inevitably be required Thus our interest in the chemistry and immunological aspects of the sputum especially when derived from asthmatics, is merely the opening phase of what must be a multi disciplinary attack on the problem of bronchial asthma These initial studies are concerned with those cases of the asthmatic syndrome marked by the intrabronchial accummulation of characteristic thick gummy viscid mucus While this has long been recognized as a characteristic defect of intrinsic (or infective) asthma it is by no means confined to this syndrome and may frequently be encountered in other chronic diseases of the respiratory tract The extraordinary degree to which such mucus may obstruct airways is quite evident on examination



FIG 1 — Gross specimen of lung of patient who died in an acute asthmatic attack The forceps are holding a stretched strand of the homogeneous accellular bronchial mucus which literally filled the brochial tree (Courtesy of Merle S Shherr M D Charleston West Virginia)
(From Bukantz and Berns Studies with Sputum, I J of Allergy 29 29 43 1958)

of the lungs of patients who have died in asthmatic attacks Figure 1 illustrates a gross specimen of such a patient

At about the same time as our studies were initiated Werner published an extremely extensive study of the glycoproteins derived from mucus epithelium and epithelial secretions throughout the body His section on the respiratory tract reviewed the rather meager data on the chemistry of respiratory secretions which preceded his own work For example Muller had in 1901 applied a complex purification procedure to sputa collected

from patients suffering from various kinds of bronchopulmonary disease
containing
id hydro
by paper
chromatography the presence of galactose in this material All of three specimens obtained by Werner from a person suffering with acute bronchitis contained hexosamine galactose fucose and traces of mannose Neither sulfate ester groups nor hexuronic acid were found in any of the specimens There were no unusual features on amino acid chromatography of one of the sputum specimens except for the possible presence of increased amounts of threonine and phenylalanine The latter finding prompted Werner to hypothesize that these particular amino acids might be involved in conjugation with the polysaccharide moiety although he did not venture an opinion as to the nature of such bonds Neither Werner nor Muller made any observations on the biologic activity of their preparations although Werner had recognized that the basic structure of the glycoprotein of epithelial

possibility that blood group substance itself might be responsible for the viscosity of sputum Our earlier work was concerned with the initial purification procedures and the analytical techniques which were employed in pilot studies Our first communication published in The Journal of Allergy for Jaunary 1958 described the quantitative techniques employed in an analysis of the combined alcohol precipitates from 28 sputa Briefly these methods consisted of the precipitation of the individual sputa which were first percipitated at a 65 % final concentration of alcohol and then a 26 G pool of the dried powdery precipitates was prepared The individual precipitates before pooling were analyzed for carbohydrate nitrogen and hexosamine content and Table I represents the range of the constituents

TABLE I

Range of Constituents in nineteen EtOH precipitaded asthmatic sputa

From Bukantz nd B rns Stud w th Sputum I J urn l of All rgy Volum 29 No 1 P g s 29 to 43 J nuary 1958

tuents which were observed in these precipitated asthmatic spura These chemical data indicate that the major difference between the precipitable material in asthmatic sputum and the purer blood group substance is that the crude ethanol precipitates from sputum were considerably higher in

nitrogen and lower in total carbohydrate and hexosamine Two dimensional chromatograms of 18 hour 6 normal hydrochloric acid hydrolysates of the alcohol precipitates failed to yield any evidence of distinctive differences among the various sputa and the amino acid patterns were those typically observed with proteins It was however, of some interest that all of the hydrolysates yielded rather higher concentrations of threonine and phenylalanine than are encountered with similar chromatograms of ordinary protein hydrolysates This latter finding is in agreement with Morgan s observations with human A V and O blood group substances One dimensional chromatograms of 2 hour 2 normal sulfuric acid hydrolysates prepared for carbohydrate analysis showed the presence of galactose mannose fucose and hexosamine the latter not yet having been further identified Thus the same individual monosaccharides were identified as are found in hydrolysates of blood group substance The results of chromatographic analysis also revealed that non blood group substance protein is present in the ethanol precipitates This observation is based upon the demonstration of considerable amounts of the aromatic amino acids (phenylalanine and tyrosine) in the hydrolysates of sputum and the relative absence of these from similar hydrolysates of the purified blood group substances

The alcohol insoluble residues failed to dissolve readily when rehydrated and there was considerable variation in the degree of viscosity which developed after rehydration For this reason additional fractionnation was attempted and the pepsin digestion phenol extraction method was selected

mucus Our first paper indicated that by the application of these methods we were able to obtain in low yield a viscous water soluble phenol insoluble fraction The yield of this material on a weight basis was not appreciably greater than that which could be obtained by direct phenol extraction alone Table II summarized the chemical data which characterized the various sputum fractions which we obtained It will be noted from this table that only the phenol insoluble fractions (PPI and PPI 50) and especially the 50 % alcohol insoluble portion (PPI 50) yield data comparable to that for blood group substance It is of interest that the ratio of hexosamine to total carbchydrate was little affected by the purifying procedures which suggested that the carbohydrate moiety of the original ethanol precipitate

buffer By contrast
(Figure 2) Althougl
phoresis they did mo
tours and mobilities differed from commercial A (hog) and B (horse) purified blood group substances These data suggested that there might be differences between the blood group substance of commercial animal origin and that derived from asthmatic sputum A pepsin digested and phenol extracted fraction derived from sputum although extremely active in hemagglutination inhibition (Table III) was nevertheless devoid of anti

TABLE II

Summary of chemical data of sputum fra tions

SAMPLE	PER CENT TN	PER CENT TC	PER CENT HEXOSAMINE	RATIO HEXA TC	PER CENT FUCOSE	PER CENT N ACETYL	RELATIVE VISCOSITY
CI	9 8	16 9	8 3	0 49	5 14	3 7	—
PEtOH	6 5	37 1	18 0	0 49	10 0	7 5	—
PPS 30	8 0	31 3	18 0	0 58	6 2	8 4	1 53
PPI	3 9	31 7	20 9	0 66	10 7	8 9	1 41
PPI 50	5 3	39 5	22 3	0 57	16 4	10 8	2 69
A (1)	6 4	43 5	28 1	0 65	5 8	14 1	—
A (2)	5 9 to 6 4	55 to 61	30 to 34	0 54 to 0 60		9 1 to 11 3	1 39 to 1 71
A (3)	5 7 to 6 4	42 to 52	24 0 to 27 3			9 6 to 10 7	2 80 to 2 86
B (1)	6 2	33 4	23 8	0 71	6 5	12 5	
B (3)	4 8 to 4 9	53 9 to 55 1	20 3 to 22 7	0 38 to 0 41	19 7 to 20 2		
O (2)	5 9 to 6 1	56 to 59	32 to 34	0 55 to 0 57		9 3 to 10 2	1 47 to 1 63

(1) = Washington Univer ty analyai of Sharp & D hn A and B ub tanc
(2) = K b t analy f pu fied A nd O ub tan
(3) = M rgan analys s of pu fied A and B substanc
TN = T tal N t ogen
TC = Total Carbohydr te

From Bukantz and Berns Stud s u th e

genicity when injected intravenously into rabbits And in this respect, it resembled purified commercial blood group substance and differed from whole sputum which proved to be quite antigenic

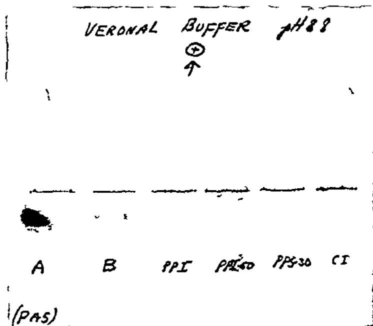


Fig 2 — Paper electrophoregram of A and B blood group substances and sputum fractions stained with periodic acid Schiff reagent. Run for six hours at 350 volts and 4 to 5 Ma.
(From Bukantz and Berns Studies with sputum I J of Allergy 29 29 43 1958)

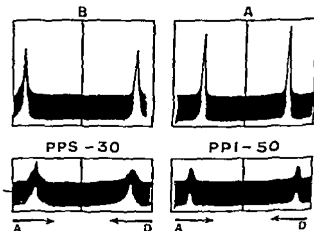


Fig 3 — Free electrophoresis of commercial A and B substances PPS 30 and PPI 50 mobilities respectively 1 51 × 10⁵ 13 37 × 10⁵ and -0 28 × 10⁻⁵ cm/sec/volt From Bukantz and Berns Studies with Sputum. I J of Allergy 29 29 43 1958

TABLE III

*Determination of blood group activity of sputum fraction by inhibition of hemagglutination of A and B cells**

MCG ADDED	A CELLS													B CELLS†												
	100	50	25	10	5	1	0.5	0.1	0.05	0.01	0.005	0.0005	0.00005	100	50	25	10	5	1	0.5	0.1	0.05	0.01	0.005	0.0005	0.00005
A substance***	—	—	—	—	—	—	—	—	—	—	1+	2+	3+	3+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+
B substance***	—	—	—	—	—	—	—	—	—	1+	2+	2+	3+	—	—	—	—	—	—	1+	1+	2+	2+	3+	3+	3+
PPI	—	—	—	—	—	—	—	—	—	—	1+	2+	3+	—	—	—	—	—	—	—	1+	1+	2+	3+	3+	3+
PPI 50	—	—	—	—	—	—	—	—	—	—	—	2+	3+	—	—	—	—	—	—	—	1+	1+	2+	3+	3+	3+
PPS 30	—	—	—	—	—	—	—	—	—	—	1+	2+	3+	—	—	—	—	—	—	1+	1+	1+	2+	3+	3+	3+
PEtOH	—	—	—	—	—	—	—	—	—	—	1+	2+	3+	—	—	—	—	—	—	—	—	—	—	—	1+	2+
CI	—	—	—	—	—	—	—	—	—	—	—	2+	2+	—	—	1+	1+	2+	2+	2+	2+	3+	3+	3+	3+	3+
Ragweed pollens****	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	—	—	—	2+	2+	2+	2+	3+	3+	3+	3+	3+	4+
Saline	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+

Commercial human blood typing sera (Michael Reese) 0.1 ml antigen plus 0.2 ml serum dilution plus 0.1 ml 4 per 100 RBC
1+ 2+ 3+ 4+ denote complete strong moderate slight and no inhibition respectively
A and B blood group substances kindly furnished by Dr R T Smith Sharp & Dohme
Quantities of extract designated as protein nitrogen units

From Bukantz and Berns Studies with Sputum I Journal of Allergy Volume 29 No 1 Pages 29 to 43 January 1958

These initial observations performed with a pooled preparation of numerous ethanol precipitates were extended by the application of the same immunochemical procedures to individual specimens of asthmatic sputum and bronchial mucus derived from patients suffering non asthmatic

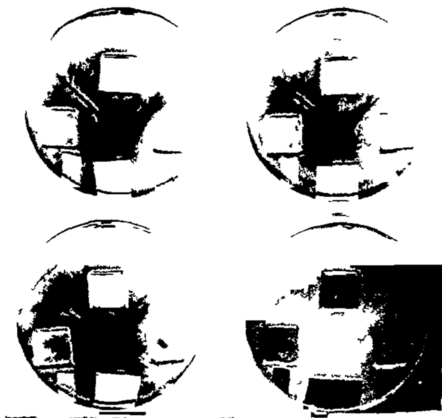


FIG 4 — Photographs of gel diffusion of sputum from asthmatic subjects type A (RG) (GO) B (PW) O (MJ) vs rabbit antiserum (RARG) to sputum from A subject RG

diseases Sputum preparations were prepared sterilely and were used to immunize rabbits either in saline suspension or after mixture with Freund s adjuvants Anaphylaxis was encountered early in the course of immunization and the animals surviving an initial course of injection were bled after having received as little as 17 mg of the sputum solids in 10 intravenous injections Antisera from these animals (RARG) which had been immunized with sputum from an A subject agglutinated A erythrocytes to high titer B and O erythrocytes to a lesser degree and produced multiple bands of precipitation in agar gels when diffused against sputa derived

produced no bands with 8 individual human serums as antigens nor with soluble extracts of all the bacteria common to the bronchial flora An incidental finding of considerable interest was the fact that distilled water

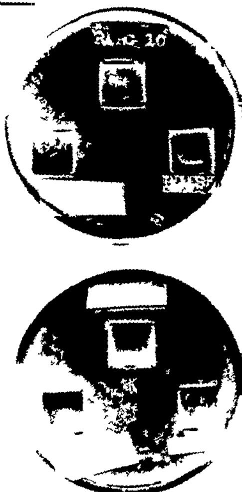


Fig 5 — Photographs of gel diffusion of RAWG s 1 8 dilution of A and B lysates paired with homologous sputum RG

lysates of A B and O erythrocytes yielded precipitate bands in agar gels with RARG and reactions of identity when paired with sputa of O A or B subjects in all combinations although specific reactions remained for each lysate (Figure 5)

After absorption of A B O agglutinins from RARG with corresponding erythrocytes precipitins for the lysates and sputa were of diminished intensity Arthus skin reactions were elicited in the immunized rabbits

tested with hog and horse blood group substances and homologous sputum antigens Tests with heterologous sputum antigens are in process In general rabbits immunized with sputum suspended in Freund s adjuvants in our first courses of immunization failed to develop agglutinins regularly nor did their skin tests become positive Preliminary studies on the avidity of the rabbit antisera in the agglutination of human erythrocytes indicate that they are at least as avid or more avid than commercial human isoag glutinins employed in the blood group agglutination procedure This is of course a matter of more than passing interest to the hematologist and very worthy of further exploration

Blood group substance obtained by purification from whole sputum by the methods previously used by Morgan and Kabat with their material from animal sources failed to immunize rabbits to the production of hemaggluti nins when an identical course of immunization with the purified product was carried out This observation is similar to that previously described by Baer who found that human pseudo mucinous cyst material was wholly antigenic when injected into rabbits whereas the purified material derived therefrom was itself non antigenic though still active as a hapten

The observations to date have simply scratched the surface and are useful mostly in pointing up the desirability of extending studies on the chemistry and immunochemistry of the sputum from asthmatic subjects Most students of the asthmatic state are agreed that a genetic factor is of impor tance in the predisposition to its development and the careful analysis of blood group factors affords an excellent opportunity to study at least one of the important genetic manifestations in relationship to the disease Furthermore advantage may be taken of the demonstrated antigenicity of the sputum itself to adapt immunological procedures to a more detailed study of the cellular sources responsible for the production of the abnormal material (or the abnormal quantity of a normal material) At the present time for example studies in progress are concerned with the preparation of fluorescein conjugates of various antisera to sputum These conjugates are being used to label various antigens of sputum in their intracellular location in an imm
nature of the sputu
chemical substance
in the development of techniques and methods of purification which may permit a more precise analysis of the various elements which are involved in sputum production and particularly in the differentiation of normal and diseased states

SUMMARY

Interest in the chemical nature of bronchial mucus developed in part to ascertain whether differences exist between normal mucus and that asso-

we found that asthmatic sputum contained hexosamine n acetylhexosamine and fucose and was devoid of uronic acids and nucleoprotein A large part of sputum appeared to be a mucopolysaccharide which could be purified by methods used for isolating blood group substance Isolated sputum frac tions were very active in hemagglutination inhibition and were apparently of broad specificity

Sterile suspensions of whole sputum were antigenic in rabbits inducing anaphylaxis in some Antisera were obtained which agglutinated homolo

substance obtained by purification of whole sputum failed to immunize rabbits confirming earlier observations of Baer et al that human pseudo mucinous cyst material was wholly antigenic when injected into rabbits while the purified material derived from it was non antigenic though still active as a hapten

An extension of these studies is in progress to ascertain the nature of the chemical composition of the sputum the possibility that anormalities exist in such disease states as asthma and the cellular origin of the mucus in normal and diseased states In these current investigations fluorescein

RÉSUMÉ

Il est interessant d etablir quelles differences peuvent exister entre le mucus bronchique normal et celui que l on rencontre au cours de diverses maladies Il semblait aussi utile d etre renseigne sur les mecanismes physiologiques qui conditionnent l accumulation des secretions bronchiques

Confirmant les precedentes observations faites par d autres auteurs sur le mucus epithelial d origines diverses nous avons constate que l expec toration des asthmatiques contient de l hexosamine de la n acetylhexo samine et de la fucose et ne renferme ni acides uroniques ni nucleopro- teines Une partie importante de cette expectoration est constituee par un muco polysaccharide que l on pourrait purifier par les methodes employees pour isoler les substances des groupes sanguins Des fractions isolees de l expectoration exercent une action inhibitrice intense sur l hémo aggluti nation et semblent presenter les caracteres d une large specificite

Des suspensions steriles de l expectoration totale ont montré chez des lapins une action antigenique et ont provoque des reactions anaphylactiques chez certains d entre eux Les auteurs ont obtenu des anti serums doues d un fort pouvoir agglutinant a l egard des erythrocytes homologues et heterolo gues et produisant de nombreuses bandes de précipitation en milieu gelifie avec des expectorations prelevees chez des asthmatiques du groupe O A et B Des lysats provenant des erythrocytes A B et O produisent des bandes de precipitations avec l anti serum de lapin sensibilise avec les expectora tions des asthmatiques

Des substances specifiques des groupes sanguins obtenues par la purifi cation d expectoration totale n ont pu immuniser les lapins Ces resultats confirment les experiences de Baer et Coll montrant que les substances pseudo mucineuses provenant de kystes humains sont antigéniques lors qu on les injecte telles quelles à des lapins alors que purifiees les produits qui en derivent ne sont pas antigeniques mais ils exercent leurs actions commehaptenes

Des etudes sont en cours ayant pour but de déterminer la composition chimique de l expectoration des anomalies dans les cas d états pathologiques tels que l asthme et l origine cellulaire du mucus tant dans les etats nor maux que dans les etats pathologiques

Au cours de recherches actuelles nous préparons des conjugues de fluo rescéine avec les globulines isolees de l antiserum de lapin traité avec l expec toration totale d asthmatique et aussi avec les isoagglutinines humaines Nous employons ces conjugués pour la coloration du tissu pulmonaire preleve chez des individus normaux et asthmatiques soit en utilisant un cryostat soit des coupes a l aide d un microtome à congelation Les résultats de ces recherches seront rapportes

ZUSAMMENFASSUNG

Es zeigte sich Interesse bezuglich der chemischen Natur des Bronchial schleimes um so fest zustellen ob Unterschiede zwischen normalem Schleim und dem Schleim bei verschiedenen Krankheilen bestehen Man wollte auch [illegible] kennenlernen denen die intrabronchiale [illegible] ebereinstimmung mit den Beobachtungen [illegible] ithelialen Schleimproben verschiedenen Ursprungs fanden wir dass das Sputum bei Asthma Hexosamin n Acetyl hexosamin und Fucose enthalt Uronsauren und Nucleoproteine aber fehlen Ein Grossteil des Sputums scheint aus einem Mukopolysaccharid zu bestehenn das wir mittels der zur Isolierung der Blutgruppensubstanzen verwendeten Methoden rein darstellen konnten Isolierte Sputumfraktionen hemmen sehr aktiv die Hamagglutination und scheinen von einer breiten Spezifitat zu sein

Sterile Suspensionen des Gesamtsputums sind antigen fur Kaninchen und erzeugen bei manchen eine Anaphylaxie Es konnten Antiseren erzielt werden die homologe und [illegible] agglutinieren und die vielfacl [illegible] wenn sie gegen die Sputa vor [illegible] Destillierte Wasserlysate von [illegible] Prazipitationsbander mit Kaninchen Antisputums Seren Die aus dem Gesamtsputum rein dargestellten Blutgruppensubstanzen konnen Kaninchen [illegible] antigen waren wohl aber als Haptene wirkten

Erweiterungen dieser Studien sind im Gange um die Natur der chemis chen Zusammensetzung der Sputa zu ermitteln weiters die Moglichkeit von Anomalitaten in Krankheiten wie Asthma festzustellen und den zellularen Ursprung des Schleims bei normalen und kranken Personen kennenzulernen

Bei diesen laufenden Untersuchungen werden Fluorescein Koppelungen mit den Globulinen der Kaninchen Antisputum Seren und menschlichen Isoagglutininen angestellt und die gekoppelten Antikorper werden zum Farben von normalen und krankhaften Lungengewebe verwendet das entweder im Kryostaten oder mittels der Gefriertrockenmethode praparıert wurde

RESUMEN

El interes en la naturaleza química del mucus bronquial se ha originado en parte para verificar si existen diferencias entre el mucus normal y el producido durante ciertas enfermedades asi como para estudiar los meca nismos fisiológicos responsables de su acumulación en los bronquios El autor ha confirmado la presencia en el esputo asmático de hexosamina n acetilhexosamina y fucosa y la ausencia de ácidos uronicos y nucleo proteinas en concordancia con los resultados obtenidos por otros investiga dores en mucus epiteliales de distintas fuentes Ha encontrado también una buena cantidad de mucopolisacáridos que pueden ser purificados con los metodos utilizados para aislar las sustancias antigenicas que determinan los grupos sanguíneos las fracciones encontradas poseen una especificidad relativa y son muy activas en la inhibición de la hemaglutinacion

Las suspensiones esteriles de esputo son antigénicas en conejos y en algunos casos producen fenómenos de anafilaxia Los antisueros obtenidos aglutinan con un título elevado los globulos rojos homologos y heterologos y producen bandas multiples en gel de agar cuando se los ensaya contra esputos de pacientes asmaticos de grupo O A y B Las bandas tambien se obtienen con los sueros de conejo anti esputo y los dialisados contra agua destilada de globulos A B y O La sustancia especifica obtenida por purifi cación de los esputos es incapaz de inmunizar a los conejos en confirmacion con los resultados de Baer et al quienes encontraron que el material prove niente de quistes humanos era antigenico para el conejo no asi los productos de pruificacion del mismo que solamente poseian caracter de haptenes

El autor se refiere a las investigaciones en curso de ejecucion sobre la composicion quimica del esputo la posibilidad de anomalías en esta compo sición durante el asma y otras enfermedades y el origen celular de los compo nentes Estas investigaciones se estan realizando con ayuda de sustancias marcadas con fluoresceina A tal efecto se utilizan las globulinas del suero de conejo anto esputo y las isoaglutininas humanas cuya fijacion se estudia luago *en tejidos pulmonares*

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(For a complete bibl ography of the literature c ted)

ACKNOWLEDGEMENTS

This work was made poss ble by the invaluable efforts of my Research Ass stant Mrs Aline W Berns We are both greatly indebted to Dr Sam Frankel for his guidance in all the chemical aspects of this work

RECENT ADVANCES IN THE PSYCHOSOMATIC CONCEPTS OF CLINICAL ALLERGY

by

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In 1905 Sigmund Freud (11) published a report under the title Fragment of an Analysis of a Case of Hysteria Since then the report has become better known as The Case of Dora the name Freud gave to the young girl who provided the clinical material for his report In the course of

of their affection is lavished on her once more whenever she arouses their

to make in her childhood countered owing to her marriage with an inconsiderate husband who may lavish neither his affection nor his money upon her In that case ill health will be her one weapon for maintaining her position It will procure her the care she longs for it will force her husband to make pecuniary sacrifices for her and to show her consideration as he would never have done while she was well and it will compel him to treat her with solicitude if she recovers for otherwise a relapse will threaten Her state of health will have every appearance of being objective and involuntary—the very doctor who treats her will bear witness to the fact and for that reason she will not need to feel any conscious self reproaches at making such successful use of a means which she has found effective in her years of childhood

Thus in one brief paragraph Freud has depicted the neurotic needs which lead to psychosomatic illness It is of interest that he chose a case of clinical allergy as an example for there is considerable evidence that Dora s respiratory symptoms such as attacks of shortness of breath spells of spasmodic coughing and hoarseness to the point of aphonia might well fall under this head

The psychological motivation behind Dora s illness as Freud points out was the need to obtain love from her parents In other words the child felt that she had been deprived of love Later David Levy (1937) (22) was to apply the term affect hunger to the striving of the child who feels rejected Meanwhile Edoardo Weiss (38) in 1922 in his discussion of a case of asthma which he had treated psychoanalytically came to the conclusion that asthma is brought on by fear of separation from the mother that it is actually a manifestation of the striving for love or as Levy put it, a striving to satisfy affect hunger

French and Alexander (10) in 1941 elaborated on this hypothesis They agreed that the attack of asthma is set off by the desire for love but that the asthmatic attack also expresses the fear that it will not be forthcoming They graphically described the asthmatic attack as a suppressed cry for the mother thus recognizing that there is in it an element of emotional repression. Apparently the asthmatic has the need to hide his affect hunger and his fear of rejection both from himself and from his parents

The question arises Why should these emotions have to be hidden? The answer lies in the unconscious and seldom recognized anger which the asthmatic feels toward his mother It is the unconscious fear that this anger will be exposed that dictates the intense emotional repression under which the asthmatic functions

Many investigators have sought the reason for the anger of the asthmatic toward the mother and have come to the conclusion that it stems from the mother s attitude toward the child For instance Gerard (1953) (12) in her report on five cases of bronchial asthma which she had treated psychoanalytically speaks of them as being mothered by dependent demanding ungiving mothers Two of Gerard s mothers said they shook the baby out of crying another beat him another said she left him alone until he stopped crying Miller and Baruch (1948) (26) have observed similar attitudes of maternal rejection by the mothers of asthmatic children They found also (1950) (27) that despite a realistic basis for anger toward the mother the asthmatic children as opposed to a control group of non asthmatic children sought to hide and disguise their anger They feared that its discovery would lead to still further rejection of them

Just as it is often difficult to uncover the anger which the asthmatic feels toward his mother it is difficult to uncover the feeling of rejection which the mother feels toward the asthmatic child As was shown by Levy (1931) (23) maternal rejection is often disguised behind a reaction formation leading to what he called maternal overprotection But there remains one group of mothers as described first by Sperling (1950) (34) and later by Abramson (1953) (1) and by Jessner (1955) (17) who apparently deeply love their children As Jessner says of this group The asthmatic child assumes a special place in his mother s feelings She unconsciously regards the child as part of herself without which she feels incomplete These feelings are derived from her own past Often she has turned away from or been disappointed in her own mother But the unconscious need for the mother persists With the child they repeat the symbiotic relationship with the mother figure The still active conflict between closeness and distance is transferred to him The child responds in kind He feels the wish for closeness and protection and at the same time the drive toward

independence and growth. He feels enveloped and choked by his mother's need to keep him so close. This is often expressed symbolically in his fantasies in the imago of a claustrum or womb which is both an inviting shelter and a dangerous trap. For both the mother and child the asthma itself may become a vehicle for the expression of feelings of protection and rejection, surrender and rebellion. This conflict is intensified when the child is with his mother and lessened when he is away from her. To the child the mother's attitude appears to be essentially a denial of him as a separate entity. To him it spells rejection and his response is anger just as anger is the response when the rejection is more direct.

No matter how the anger is engendered in the child or in the child grown into adult it must find an outlet. As Bacon (1956) (3) has shown not only do patterns of neurotic behavior serve this purpose but the asthmatic attack itself is often a disguised expression of hostile aggression. That this holds

[illegible]

They have also found that all the allergic syndromes represent repression of the same three emotional forces which have been discussed: the hunger for love from the mother, the fear of loss of the mother and the anger at the mother.

Why a particular allergic syndrome is used has not yet been determined. Nor are we certain why the repressed emotional forces find somatic expression in allergic syndromes instead of in other psychosomatic illness. Most investigators support Alexander's (1950) (2) hypothesis of a constitutional X factor. As allergists we prefer to designate this factor as the allergic constitution.

The allergic constitution is generally considered to be genetically determined. It is accompanied by certain characteristic but abnormal somatic and psychological attributes. Among these somatic attributes is the capacity to produce specific abnormal antibodies (reagins) to proteins commonly found in the diet and the environment. Another is the capacity to react with an abnormal respiratory response such as bronchial asthma to real or imagined threats to the respiratory system. The allergic constitution also appears to carry with it certain emotional reactions which depart from the normal. How far these are genetically determined is still a moot question. For the most part they seem to arise from realities of life experienced by the allergically constituted individual in the climate of maternal rejection. As a result there arises an intense hunger for love, an abject fear of losing the mother and inordinate anger at the mother. As a result there are exorbitant expenditures of both psychic and physical energy in repression of such emotions.

It would seem that with so specific a psychodynamic pattern definite personality types as postulated by Dunbar (1943) (9) would be found among allergic individuals. Other investigators such as Kubie (1954) (19) and Leigh (1953) (21) however
thesis is apt to be misleadin
suffering from allergic disea
themselves in personality patterns, behavioral patterns and somatic illness

patterns vary from individual to individual despite the fact that the same emotional tensions may initiate them For example the repressive manœuvers of the allergic may vary from an apparent independence that is so aggressive as to make the presence of an underlying dependency seem ridiculous On the other hand, they may lead to a surrender to illness so abject that it can be figuratively described as a return to the womb For both diagnosis and therapy it is therefore important that these varying displays of personality be recognized as defenses in order that the underlying true emotional factors are not overlooked

co1

emotional tensions which set them off

As has been shown the basic yearning of the allergic individual no matter his age (Alexander and Visotsky 1955) (3) is for mother love As a result (Saul and Lyon 1954) (32) there will be forces at work within the individual pushing him in the direction of regression He has the hope that by seeking an earlier stage of life he will find the love that he has missed or feels he has missed It is in these strivings or regression that we may find a clue to the varying choices of somatic and emotional symptoms The asthmatic syndrome for example may represent as Wolf et al (1950) (41) have demonstrated a protective adaptive reaction determined by the allergic heredity It is an attempt to keep some noxious agent out of the respiratory tract and to wash away what is left of it Saul and Lyon (N D) (32) have added that the threat may not necessarily be to respiration but because of a common physical ontogeny the threat may be to the gastro intestinal tract leading to fear of poisoning Or by a common psychological ontogeny to any part of the body including the excretory and sexual ones

The ultimate in regressive wishes of course is to actually return to the womb But even this pleasant fantasy by those asthmatics whom Deutsch (1955) (8) pertinently calls water babies often becomes frightening As Bacon (1956) (5) has noted the asthmatic may associate drowning suffocating in a dark confined space and even being eaten up with the fantasy of

or ointment may bring on an exacerbation of eczema to achieve this end Yet the fantasy of wanting to eat up the mother to scratch with talon teeth fingernails to punish her or to incorporate her may lead to the same sort of skin eruption The hostile fantasy of the eczematous allergic that he is a dirty baby who will thus punish the mother may also contain the erotic fantasy of bodily contact with the mother

To recapitulate briefly it may be said that the neurotic individual with an allergic constitution attempts to relieve his tensions achieve homeostasis (Kubie 1948) (20) not only by psychoneurotic patterns of behavior chiefly repressive and regressive but also by patterns of disturbed physiology suited to the era to which regression is desired These disturbances are the syndromes of clinical allergy

It may have been noted that the point of view here has been to consider the allergic disturbances as a form of acting out by the body In other words to treat them as though they were hysterical conversion symptoms an

attempt to relieve emotional tension in a symbolic way Classically this has meant that such symbolization can be expressed only through the voluntary nervous system both motor and sensory As Alexander (1950) (2) and Szasz (1951) (36) have pointed out those psychosomatic diseases that are manifested through somatic phenomena mediated only through the autonomic nervous system e g psychogenic peptic ulcer should not properly be considered as a symbolic expression of the emotion but its normal physiologic concomittant. They both speak of these as *organ neuroses* or as partial and specific regressions as opposed to conversion hysteria Groen (1957) (14) prefers to include both organ neuroses and conversion hysteria under the term Psychosomatic patterns of abnormal behavior Stockvis (1937) (35) includes all diseases with either etiologic or otherwise related emotional factors as psychosomatic diseases but follows Halliday (1945) (15) in classifying the organ neuroses as *somato neuroses* including asthma among them

It may be said with Alexander (1950) (2) that we live psychosomatically and therefore, as the present authors agree all disease is psychosomatic It is for this reason that it becomes important to seek the relationships which exist between the psyche and the soma not only for each disease but for each individual who suffers from that disease In the allergic diseases the authors believe that the initial somatic symptoms are frequently hysterical

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control but with a physiologic function respiration which is also partially *under control of the voluntary nervous system One may surmise that the* respiratory system is capable of feed back mechanisms between the voluntary and the autonomic nervous system which may go on circularly and indefinitely Such a possibility is confirmed clinically when one sees that an asthmatic can set off a typical asthmatic attack essentially an autonomic phenomenon with a cough that is wholly voluntary The asthmatic can also set off an attack by voluntary over ventilation and as Dekker and Groen (1957) (7) have shown by voluntary increase of intrathoracic pressure Dekker and Groen explain the wheezing respiration during voluntary increase of intrathoracic pressure as due to prolapse of the soft tissues of the trachea and larger bronchi into their lumens producing mechanical obstruction This does not explain the persistence of the wheezing dyspnea when an asthmatic makes the voluntary effort The asthmatic continues to wheeze because the original obstruction of the airways has set off an abnormal autonomic response but one that is characteristic for the asthmatic in the face of any real or fantasied threat to the respiratory apparatus The feedback mechanism which causes the asthma to persist is therefore both

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It is also a psychological syndrome with repression of the emotions Since the emotions repressed or blocked are those which express dependent regressive needs Alexander (1950) (2) and Szasz (1952) (37) postulate that the parasympathetic nervous system is used to express such blocked energy

The other allergic syndromes are also examples of parasympathetic physiological disturbances but as Grinker (1953) (13) states both voluntary involuntary and parasympathetic sympathetic processes are in constant phasic and cooperative activity The danger in giving a unidirectional explanation of psychosomatic functioning is further emphasized by our knowledge that under hypnosis the dividing line between autonomic and voluntary functions appears to disappear This seems to be the case also with certain individuals who have trained themselves so that they can voluntarily control some autonomic functions Anatomically Magoun (1952) (25) is inclined to recognize in the reticular system of the brain connecting links between the voluntary and the involuntary nervous systems

Although the various facets of psychosomatic functioning often seem disparate and even unrelated yet there is a basic relatedness in all the conceptualizations in this field a consistency that derives from the modern understanding of the psychodynamics of the human being In the field of clinical allergy the knowledge of the fundamental relatedness between psyche and soma has enabled many workers to achieve a considerable degree of success with the various types of uncovering psychotherapy which have been attempted in recent years The principles on which uncovering psychotherapy is based essentially the uncovering of etiologic life experiences and fantasies and their interpretation direct treatment at those emotional components of the allergic diseases as have been here discussed central to which is the mother child relationship

One wonders why in all of this discussion concerning etiology the father s role has not been considered more critical

We might exclaim with Dawes (1953) (6) in her discussion of Gerard s cases when she says to my surprise the fathers were not mentioned by Dr Gerard But doesn t the father also influence the mother child relationship? Many young fathers are intensely jealous of the baby They resent it and are openly hostile when the mother cares for the baby It is as if the father wanted to be the baby himself

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to assume a father role It fits in also with Grinker s (1953) (13) broader statement that many fathers of today fail to save the child from the possessive and infantilizing role of the mother so that the father is simply not the dominant or co dominant factor in child development or discipline He cannot be depended on as a source of strength Psychotherapy which

based as it is on the recognition of the importance of the mother in the mother child relationship This Sperling terms indirect treatment

A variant of this is the treatment by separation as described by Hallowitz (1954) (16) at the National Jewish Home for Asthmatic Children Here he children were removed from the real, rejecting parents to surrogate

accepting parents at he Home In many instances there resulted relief from symptoms as might be anticipated from Jessner s (1955) (17) observations on the symbiotic relationship often found between the mother and the asthmatic child But it was also found that many of the children relapsed on being returned to their parents or when the parents came to visit them Such relapses have been materially lessened since group and individual psychotherapy has been undertaken with the parents during the absence of the child

Although indirect therapy involving the parents alone is often suc cessful direct therapy with children without therapy of the parents is gene rally unsuccessful

As for individual psychotherapy with adult allergics this ranges from psychoanalysis carried out with strict adherence to classic principles through short term therapy as described by Alexander and French (1946) (4) and other modifications of individual psychotherapy such as the sector analysis (goal restricted) of Deutsch (1955) (8) with his method of associative anamnesis and the anaclitic therapy of Margolin (1953) (24) All these are fundamentally Freudian in concept and are consciously directed at resolving the repressing regressive meaning of the emotional and somatic patterns of the allergic patient The anaclitic therapy of Margolin based on his theory that psychosomatic symptoms are regressive psycho physio logical states purposely seeks to actually regress the patient to an infantile acting out of his fantasies by satisfying as far as possible all his narcissistic demands and then to rebuild ego strength from the infantile level to the mature one by teaching the patient that he can get along without his emo

[illegible]

is group psychotherapy The objectives are the same in both as are the underlying psychoanalytically oriented psychodynamic theories Both seek to remedy the distortions in the basic mother child relationship to bring affect hunger into realistic bounds to build ego strength so that fear anxiety and anger do not motivate a kind of acting out in self destructive somatization of symptoms In other words the concepts of maternal rejection with resultant affect hunger fear of loss of the mother and anger at her and the need to repress these emotions are the guideposts for much of the recent formal psychotherapy of allergic diseases Formal psycho therapy is however not always available to the allergic individual or by the allergist yet the same concepts can be used by the allergist in his day to day practice

As the allergist establishes rapport with his patient he can venture to reassure those allergics who seem to need it with more than the usual attention and warm understanding thus feeding the affect hunger by being a good surrogate mother He can further allay anxiety over possible loss of the mother by being consistent in his attitudes and by avoiding any act or remark that might convey to the allergic individual the feeling that he is being rejected Lastly when the patient seems ready the allergist may venture to elicit some expressions of hostility from the patient by indicating that he understands that there are times when everyone gets angry that

sometimes his anger is directed at the one he loves most and that there are ways of getting out the anger which are not frightening or destructive. Those are achieved chiefly by talking to the physician or in the case of children by play drawing and other technics which can be carried out in the office or in the child s home All of them if carried out in a benign non probing and non condemnatory atmosphere may provide much of the emotional strength which the allergic patient needs to get well

SUMMARY

The psychosomatic concepts of clinical allergy are an outgrowth of the theories concerning the unconscious by Sigmund Freud and more recent discoveries regarding the relations between the psyche and the soma. Allergic diseases provide a fertile field for observation and the development of newer concepts of this relationship Specifically they are an expression of both hysterical conversion symptoms and what have recently been called organ neuroses One often sets off the other and both are the result of emotional conflicts Their character is determined by the underlying allergic constitution

Apparently the most important etiologic factor in the development of emotional disturbances which finally result in physiological disturbances which are recognized as clinical allergic syndromes is fear of losing the mother s love This engenders anger usually directed at the mother which in turn has to be suppressed since its discovery might lead to further deprivation of mother love The physical manifestations of these supposed emotions are expressed through the parasympathetic nervous system.

Recent objectives in psychosomatic therapy of the allergic diseases is directed not only at the physical etiology both specific and general but also [illegible]

physical symptoms Current methods in psychotherapy which apply these principles are described and discussed

RÉSUMÉ

Les conceptions de l allergie clinique du point de vue de la psychosomatique sont le prolongement des theories de Sigmund Freud sur le subconscient et aussi de decouvertes plus recentes concernant les rapports entre le psychique et le somatique

Les maladies allergiques nous ouvrent un vaste et fertile champ d observation et nous permettent de les considerer sous des angles nouveaux Elles ont specifiquement un aspect des symptomes imputables aux deux conversions hysteriques que l on a recemment nommees « nevroses organiques »

Souvent l un de ces elements vient mettre l autre en relief et les deux

resultent de conflits emotionnels Leur caractere est determine par l état allergique de base

La crainte de la perte de l amour maternel semble etre le facteur etiologique le plus important pour le développement de troubles emotionnels qui finissent par provoquer des troubles physiologiques reconnus alors comme des syndromes allergiques cliniques

Cette psychose engendre le plus souvent un etat d irritation contre la mere qu il faut faire disparaitre car s il etait connu d elle il pourrait l amener a priver le sujet de son affection

Ces manifestations physiques que l on attribue a des troubles emotionnels se manifestent par le systeme nerveux parasympathique

Notre therapie psychosomatique des maladies allergiques a pris pour objectifs non seulement leur etiologie specifique et generale mais aussi les facteurs étiologiques d origine émotionnelle

La psychothérapie est donc amenee à réduire a des proportions normales la crainte de la perte de l amour maternel l irritation qu elle engendre et a faire disparaitre cette crainte et cette irritation qui provoquent l apparition des symptomes physiques

Dans cette etude nous discutons des méthodes de psychotherapie courante dont l application découle des principes que nous venons d enoncer

ZUSAMMENFASSUNG

Die Vorstellungen uber die klinische Allergie vom Standpunkt der Psy
d Freuds uber das
die den Zusammen

weites und fruchtbares
Gesichtswinkeln aus zu
von Symptomen die auf
beiden Konversionen zuruckzufuhren sind welche man neulich organische Neurosen benannt hat

Oft lasst eines dieser Elemente das andere hervortreten und aus den beiden resultieren emotionelle Konflikte Ihr Charakter wird durch den allergischen Basiszustand bestimmt

Die Furcht vor den Verlust der mutterlichen Liebe scheint der wichtigste atiologische Faktor fur das Zustandekommen emotioneller Storungen zu sein die schliesslich physiologische Storungen provozieren welche als klinisches Allergiesyndrom in Erscheinung treten

Diese Psychose erzeugt sehr oft einen Irritationszustand der Mutter gegenuber den man zum Verschwinden bringen muss da sollte er ihr bekannt werden er die Person seiner Liebe verlieren konnte

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emotionell bedingte atiologische Faktoren

Die Psychotherapie hat also das Ziel normale Verhaltnisse wiederherzustellen die Furcht vor den Verlust der mutterlichen Liebe und die dadurch

hervorgerufene Irritation die das Auftreten von physischen Symptomen verursachen zum Verschwinden zu bringen

In dieser Studie diskutieren wir die Methoden der gelaufigen Psychotherapie deren Anwendung Grundsatze bedingt die wir besprechen werden.

RESUMEN

Los conceptos psicosomáticos de la alergia clínica son un desarrollo de las teorias de Freud sobre el subconsciente y de los descubrimientos sobre les relaciones entre la psiquis y el soma Las enfermedades alergicas constituyen un campo fertil para el estudio de estas relaciones Especificamente constituyen una expresión de síntomas de conversión histerica y de lo que ha sido recientemente llamado neurosis de organo a menudo ambas son incompatibles y como consecuencia se originan conflictos emocionales cuya característica esta determinada por la constitucion alergica

Aparentemente el factor etiológico mas importante en el desarrollo de los trastornos emocionales que conducen finalmente a los sindromes alergicos es el temor de perder el afecto maternal Ello acarrea un estado de angustia dirigido hacia la madre que a su vez debe ser reprimido para que su descubrimiento no contribuya al alejamiento maternal Las manifestaciones fisicas aparecen a traves del sistema nervioso parasimpático

La terapeutica psicosomatica actual va dirigida no solamente contra los factores etiológicos fisicos sino tambien contra los emocionales La psicoterapia por lo tanto trata de reducir a sus verdaderas proporciones las respuestas emocionales que conducen a los sintomas fisicos Los autores describen y discuten finalmente los metodos actuales de psicoterapia.

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SYMPOSIUM IV

Aspects biochimiques de l'hypersensibilité

Biochemical aspects of hypersensitivity

Biochemische Anschaungen der Uberempfundlichkeit

Aspectos bioquimicos de la hipersensibilidad

INTRODUCTION

by

Sir Henry H DALE

We have been invited by the organizers of the Conference to discuss in this Symposium the Biochemical Aspects of Hypersensitivity If we
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be prepared I think to restrict our discussion to certain special aspects of hypersensitivity and naturally to choose if we can those which will give us the greatest opportunity for considering truly biochemical evidence concerning the nature of the phenomena with which we deal

I THE HYPERSENSITIVE CONDITION

Our subject divides itself naturally into two distinct though by no means unconnected phases Let us consider in the first place the nature of the hypersensitive condition itself With regard to that condition we may usefully note I think that it can be on the one hand what we may call a *natural allergy* where the manner in which the condition has arisen may be unknown or may be attributable to some known infective or other natural accident and we should note that such natural allergies have been the subject of observation and experiment very largely in man On the other hand the condition which we are studying may be an *experimental anaphylaxis* and our evidence concerning the nature of this has by contrast and for obvious reasons been mostly derived from experiments made on the animals commonly available in the laboratory and in particular on the dog the guinea pig and the rabbit It is obviously of value for the study of the hypersensitive condition in general that we should be able to use data obtained by observations and experimental analyses of the artificially

enough On the other hand I am sure that we shall be well advised to

beware of any too facile assumption that they are actually identical, and, especially of assuming that the nature of an allergic condition seen in man can be interpreted in detail by reference to what is known of an experimental anaphylaxis from studies carried out in some other animal species A

progress of knowledge hindered by a tendency to assume that evidence produced under one set of conditions and from one animal species can safely be given such a more general application

This tendency has I think been made sufficiently clear by the controversies which have been created or promoted by the use of the same designation anaphylaxis to represent the hypersensitive conditions produced experimentally in the three species principally used for such purposes Though the condition now recognized as anaphylaxis in the rabbit was by far the earliest to be recorded—its occurrence was noticed by Magendie in 1839—it has not so far received nearly so much deliberate study by experiment as have its modern namesakes in the dog and the guinea pig which were not discovered till the early years 1902 and 1904 respectively of the present century We have looked forward, indeed to the pleasure of meeting at this Congress the venerable Professor Portier co discoverer with the late Charles Richet of the condition in the dog for which Richet coined the name anaphylaxis In all three species we are dealing of course with a condition of hypersensitiveness to a foreign antigen produced by a first sensitizing injection of it or series of such injections and the condition is in all cases such that a further injection of the same antigen given after a suitable interval excites an abnormal reaction which may even be fatal in its severity And I think that it can be further recognized that in all species this anaphylactic condition is due to the formation and location in the body of an immune reagent of the precipitin type the normal function of which is protective and only incidentally sensitizing Apart however from these fundamental resemblances I think there is abundant evidence to justify a conclusion that there are wide differences between tl
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nant fixation of the antibody to sensitive tissue cells and those on the other and who attributed it to an antibody still circulating in the blood where its encounter with the reinjected antigen was supposed to initiate a train of reactions involving also the so called complement, leading to the liberation in the blood of a poisonous product of protein cleavage a so called anaphylatoxin I must avoid involvement today with the details of that controversy I allow myself however just to refer to the rather curious fact that the evidence to support the anaphylatoxin theory was mainly produced by experiments on the guinea pig in which species the

evidence in favour of the alternative theory of sensitization of tissues by cell fixation of the antibody has always seemed to me to be specially direct and convincing and in fact seems so still I confess to being undisturbed in that conviction by recent attempts to revive the anaphylatoxin hypothesis such as that made by my friend Professor Rocha e Silva He has found rather paradoxically that a particularly potent anaphylatoxin for the guinea pig can be made from the serum of a rat—although it is peculiarly difficult to produce anything like a typical anaphylaxis in the rat itself and certainly nothing like that seen in the guinea pig When rat serum is incubated with agar agar a mixture is obtained which injected in a small

large quantities of histamine from a normal guinea pig s lung The effect upon me of this recent evidence has been merely to confirm the impression received over most of fifty years from a study of the voluminous anaphylatoxin literature. It seems to me only to demonstrate once again that the tissues of a guinea pig and its lungs in particular are singularly liable to shed their histamine and other active cell constituents with a resulting anaphylactoid reaction, when they are exposed to almost any kind of injury which can be inflicted upon them by an intravenous injection We do little or nothing I suggest to discover the nature of the anaphylactic *condition* in the guinea pig by experiments with artificial mixtures which evoke such a reaction in a normal animal our problem is to discover the nature of the change in the tissues which makes them respond to a further injection of a normally harmless protein as though it were a natural poison of this type And I still think that everything points to a predominant cellular fixation of a precipitating antibody as the main factor at least of the anaphylactic condition in this species

In the dog there is again strong evidence I think of cellular fixation of an antibody as the central factor of the anaphylactic condition In this case however the sensitization is almost restricted to the cells of one organ the liver There appears to be evidence however that the production of the primary anaphylactic reaction in the dog s liver with its typical intense engorgement, requires also the presence of the blood with its normal faculty of clotting in addition to the sensitizing antigen and the liver fixed antibody The relation between these factors seems to be still obscure and worth further exploration but the recognition of the involvement of blood in

and the very different type of reaction regarded also as an anaphylactic phenomenon in the rabbit

For so far as my limited experience of the reaction in the rabbit enables me to judge it is the result of a condition which might be regarded as almost the direct converse of that which is called anaphylaxis in the guinea pig The only evidence known to me suggesting that cells of any of the solid tissues in the rabbit are to any degree sensitized by a fixed antibody concerns reactions of the isolated heart and of the perfused blood vessels of the ear

and I must admit that I do not find either of these impressive There is strong evidence on the other hand to suggest that the anaphylactic shock in the rabbit is due to the encounter between the reinjected antigen and a specific precipitin in the circulating blood and perhaps the entanglement and injury thereby of the platelets which in the rabbit s blood, are peculiar by their abundance and by the heavy load which they carry of histamine 5 hydroxytryptamine and other directly active substances The action of such substances on the blood vessels of the lungs, and the blocking effect in these perhaps of clumps of platelets seem then to be the main cause of the right sided heart failure recognized as characteristic of what is called the anaphylactic shock in the rabbit And the contrast between this condition in the rabbit and that in the guinea pig both called anaphylaxis' is seen most clearly perhaps if we consider the conditions required for the production of what is called passive anaphylaxis in the two species When a precipitating antibody is injected into the circulation of a normal guinea pig the anaphylactic condition begins to be recognizable only after several hours and it has not attained its maximum development till 24 48 hours after the injection by which time most of the antibody has disappeared from the blood into the tissues And correspondingly, a strip of isolated plain muscle from a guinea pig such as the horn of a virgin uterus or a length of the ileum can be rendered exquisitely sensitive to an antigen by leaving it for one or two days in the refrigerator bathed in a physiological saline g
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venous injection of the antibody until this in turn has been mostly removed from the circulation and fixed by the tissues In the rabbit on the contrary the recognized method of producing a passive anaphylactic reaction is to make intravenous injections of the antibody and the antigen in rapid succession and there is no evidence that any tissue of the rabbit can be rendered sensitive to the antigen in a manner comparable to that characteristic of the guinea pig either *in vivo* or *in vitro*

So far as we can judge from evidence which is by no means yet so complete as we might like it to be the mode of sensitization in human cases whether of natural allergy or of the artificial anaphylaxis following an earlier serum injection appears to conform more nearly to that of the anaphylaxis of the guinea pig than to that of the rabbit or of the dog The direc response to the antigen given by the plain muscle of human tissues from cases of allergy has been very clearly demonstrated On the other hand the liability to sensitization of the skin and the mucous membranes seems to be perhaps specially characteristic of the human allergies though it is difficult to be sure that this may not be due to the much greater ease with which reactions in those surface tissues can be observed in man than in such an animal as a guinea pig In any case I think that we should certainly run an unnecessary risk of error and controversy if we were to conclude from evidence still inadequate that the hypersensitive condition in man corresponds in all its details to any one of the different types which have hitherto been so much more fully studied in other species

and I must admit that I do not find either of these impressive There is strong evidence on the other hand, to suggest that the anaphylactic shock

by their abundance and by the heavy load which they carry of histamine 5 hydroxytryptamine and other directly active substances The action of such substances on the blood vessels of the lungs and the blocking effect in these perhaps of clumps of platelets seem then to be the main cause of the right sided heart failure recognized as characteristic of what is called the anaphylactic shock in the rabbit And the contrast between this condition in the rabbit and that in the guinea pig both called anaphylaxis is seen most clearly perhaps if we consider the conditions required for the production of what is called passive anaphylaxis in the two species When a precipitating antibody is injected into the circulation of a normal guinea pig the anaphylactic condition begins to be recognizable only after several hours and it has not attained its maximum development till 24 48 hours after the injection by which time most of the antibody has disappeared from the blood into the tissues And correspondingly a strip of isolated plain muscle from a guinea pig such as the horn of a virgin uterus or a length of the ileum can be rendered exquisitely sensitive to an antigen by leaving it for one or two days in the refrigerator, bathed in a physiological saline solution containing the corresponding antibody and then washing it free from any excess When a guinea pig has thus become fully anaphylactic the sensitive condition can be immediately masked by a further intravenous injection of the antibody until this in turn has been mostly removed from the circulation and fixed by the tissues In the rabbit on the contrary the recognized method of producing a passive anaphylactic reaction is to make intravenous injections of the antibody and the antigen in rapid succession and there is no evidence that any tissue of the rabbit can be rendered sensitive to the antigen, in a manner comparable to that characteristic of the guinea pig either *in vivo* or *in vitro*

So far as we can judge from evidence which is by no means yet so complete as we might like it to be the mode of sensitization in human cases whether of natural allergy or of the artificial anaphylaxis following an earlier serum injection appears to conform more nearly to that of the anaphylaxis of the guinea pig than to that of the rabbit or of the dog The direct response to the antigen given by the plain muscle of human tissues from cases of allergy has been very clearly demonstrated On the other hand the liability to sensitization of the skin and the mucous membranes seems to be perhaps specially characteristic of the human allergies though it is difficult to be sure that this may not be due to the much greater ease with which reactions in those surface tissues can be observed in man than in such an animal as a guinea pig In any case I think that we should certainly run an unnecessary risk of error and controversy, if we were to conclude from evidence still inadequate that the hypersensitive condition in man corresponds in all its details to any one of the different types which have hitherto been so much more fully studied in other species

II THE HYPERSENSITIVE REACTION

Whatever may be our conclusions concerning the nature of the hyper sensitive *condition*, and concerning the different mechanisms involved in its production in the different animal species we have to consider as a separate though obviously not as an unrelated problem the mechanism of the abnormal physiological *reaction* to renewed contact with the antigen by which the presence of the hypersensitive condition is revealed This perhaps, comes more easily within the indicated scope of our Symposium as giving the opportunity for discussion of the parts played in these reactions by certain chemically definite factors such as the long known histamine and the more recently discovered 5 hydroxytryptamine which has naturally been the subject of much investigation during the pa t few years Here again I think that we should be careful not too hastily to assume that the reaction as it has been observed in one or another species can be attributed entirely to factors which happen to have been or even to factors which are ever likely to be thus chemically isolated and identified Bearing in mind the fact that the reactions which we are considering seem to be in all cases due to the effects of active substances liberated by injuries of various grades inflicted on cells of different kinds in different species—on cells which are closely associated at least, with plain muscle in the guinea pig on liver cells in the dog on blood platelets in the rabbit—it would indeed be surprising if we had to conclude that the active substances concerned in all these cases and at every stage of any reaction which may be regarded as allergic or anaphylactic were all comparable in simplicity to those which have already been chemically recognized and identified We still I think have to keep our eyes open to the possible participation in such reactions of kallikrein and bradykinin the so called substance P and perhaps of chemically even less definite cell constituents or products of proteolysis such as that described as the slow reacting substance even though we cannot yet begin with any confidence to disentangle their relations with one another or to assign to any one of them the responsibility for any particular feature or any particular pha e in the whole course of such a reaction We must look hopefully for further knowledge about them Perhaps we may be encouraged by the thought that the general resemblance between the very different actions of hi tamine in several animal species and the main symptoms of the anaphylactic reactions observed in the same species was first mentioned in public just over 48 years ago at the International Congress of Physiology held in Vienna in September 1910 and that the programme of those contributions to today s Symposium which have been notified in advance seems to show that there are still di coveries to be made even about histamine and points concerning its significance which are regarded as worthy of yet further discussion in the same connexion Histamine indeed and the modes of its release still figure prominently in any discussion of the anaphylactic and allergic reactions in all the species in which they have been studied including ma widely as they differ in detail from one animal type to another

When mu h more recently 5 Hydroxytryptamine appeared upo

scene as a physiologically active pure substance obtained, independently from sources so widely different as the serum of normal mammalian blood and the salivary gland of an octopus there were naturally high hopes among those of us who are interested in such matters that it would fill some of the gaps left still vacant by the effects of histamine in the syndrome complex of the anaphylactic and similar reactions It seems on the whole not yet to have given much evidence of activities which would qualify it to meet these expectations but its possibilities are now being studied by a veritable multitude of research workers very many times as numerous as the small company of the early workers on histamine, so that we ought to know much more about 5 Hydroxytryptamine in much less than another half century

I ought also to make brief mention of the many attempts made during recent years to elucidate the process by which histamine and other directly effective agents are liberated, to play their parts in evoking the symptoms of the anaphylactic reaction Many of such experiments have been made on blood or serum from different species and have produced evidence of a complicated series of events leading by successive stages to the liberation of a proteolytic enzyme plasmin , in such body fluids It seems to me that the chief interest of such investigations for our subject the biochemical aspects of hypersensitivity must very largely depend upon the degree to which we can safely regard them as providing an analogy for the process by which such substances as histamine are released from the protoplasm of sensitized cells Does this also involve the activation and intervention of a proteolytic enzyme? The initiation of such a process by various kinds of injury might seem to be at least as likely to occur in a vigorously metabolic protoplasm as in a serum which under normal conditions is relatively inert And the experiments of Mongar and Schild have already yielded what may be very suggestive evidence for such an analogy in demonstrating the special thermolability of the mechanism by which contact with an antigen releases histamine from sensitized guinea pig tissue whereas the effect of artificial chemical releasers is by contrast comparatively thermostable I would once more emphasize however my own view that even if more direct evidence should be obtained to show that for the liberation of the direct agents of an anaphylactic or allergic reaction the prior activation of an enzyme is required our main problem is still to discover why a process which in the normal organism may be supposed to be frequently in action in the blood with no more than physiological consequences should in the hypersensitive organism take place in or in the immediate neighbourhood of sensitive cells and then be the cause of an explosive reaction

There is one other point not explicitly mentioned in our programme but likely I think to arise at some stage or another of our discussions on which I should like to comment briefly in conclusion In recent years a number of observers Riley and West in Dundee having showing the way, have been finding very interesting evidence for the special abundance of histamine in the basophile tissue cells which were named Mast cells by Paul Ehrlich There can be no doubt about the presence of histamine in these cells in those species at least in which they have been specially examined for its presence though it should be noted that the metachro

matic basophile staining which characterises them is certainly not due to the basic histamine It may reasonably be attributed to the strongly acid heparin which the mast cells are known also to contain and which can be seen to form a metachromatic combination with toluidine blue *in vitro* Without doubting that at least some of the histamine released in some of the allergic reactions of some species may well be liberated together with heparin from mast cells I would venture in this case again to give a warning against any tendency to claim too readily a more general significance for evidence which may be found to have only a limited validity It is quite certain already that all the histamine contributing to reactions recognized as anaphylactic does not come from mast-cells in all species We have seen that conspicuous features of the reaction in the rabbit can be traced to the liberation of histamine from the blood platelets which are so specially abundant in that species and are in fact responsible for the remarkably high histamine content of its blood And so far from being basophile mast cells the rabbit's blood platelets have a fine eosinophile granulation which may perhaps, be related to the fact that histamine *in vitro* can be seen to form a precipitate with acid dyes such as eosine and phloxine Dr Riley himself has pointed out in a recent paper that there are fixed tissues also in the body, which though they appear to contain no mast cells yield plenty of histamine to the usual methods of extraction The pyloric end of the stomach is one which he quotes and I do not doubt that others could be found and I do not think that we yet have adequate evidence to justify a statement even in the case of a mast cell containing tissue that the histamine which can be extracted from it or that which is released from it in a reaction of the allergic type can be confidently attributed to the mast cells alone

SUMMARY

The title given to our Symposium entitles us to discuss on the one hand biochemical evidence concerning the nature of the hypersensitive *condition* whether of natural *allergy* or of experimentally produced and reproducible, *anaphylaxis* and on the other hand the biochemical factors in the different types of hypersensitive *reactions*

1 Hypersensitive conditions

While there is obviously a broad basis of analogy between the different types of anaphylactic sensitization as seen in different animal species there is no justification for assuming that a natural allergy as studied almost exclusively in man corresponds in all details with any one of these experimentally produced conditions The anaphylactic condition appears to be due in all cases to the presence of a precipitating antibody specific for the sensitizing antigen but differing in its distribution between the blood

plasma and the fixed tissue cells in the three species, rabbit dog and guinea pig in which the phenomena have been most fully studied

a) *Guinea pig* It will be suggested that the weight of evidence is still in favour of a predominant tissue fixation of the precipitin, as the cause of anaphylaxis in the guinea pig in spite of recent attempts to revive the theory involving the production of an anaphylatoxin by the interaction between antigen and antibody in the blood

b) *Dog* In the dog again there is evidence in favour of the fixation of the antibody to cells of the liver in particular as the cause of the anaphylactic condition though the participation of the normally coagulable blood seems to be required in some way, for the full development of the primary shockreaction in that organ in response to the antigen

c) *Rabbit* What is called anaphylaxis in the rabbit is by contrast, due to the antibody circulating in the blood where its sudden encounter with the antigen somehow causes agglutination of the platelets, which are in that species exceptional in their abundance and their content of histamine etc

d) *Man* So far as evidence can be obtained the allergy of man seems to resemble the anaphylaxis of the guinea pig more nearly than those of the other two species

2 The hypersensitive reaction

In all the species examined the direct cause of the reaction appears to be the release of pharmacodynamically active substances from cells of different types—from plain muscle cells or cells in immediate relation to them in the guinea pig from liver cells in the dog from blood platelets in the rabbit Of these substances histamine was the first to be recognized as a chemical entity and is still the one of which the action is most obviously related to the immediate anaphylactic or allergic reactions 5 hydroxy tryptamine has recently received much attention as a constituent of many cells and similarly released but the extent of its contribution to allergic reactions is not yet so clear Heparin is responsible for the loss by the blood of its clotting power characteristic especially of the shock in the dog An allergic reaction especially in its later stages has other features not produced by any of these and reasonably attributable to one or more of the active substances of a peptide nature released from cells by injury or formed by proteolytic cleavage initiated thereby We shall probably be considering evidence that the liberation of histamine and other such agents may also involve the early stages of such an enzymatic action We must bear in mind however that these substances differ in action in different species histamine for example having little action in the muridæ

We should take account also of the recent evidence that the mast cells of Ehrlich contain and can release not only heparin which can account for the basophile, metachromatic staining of their granules but histamine Here again we must be careful not to give an exclusive significance to its presence in these cells there are certainly other cellular sources of histamine in the body such as the blood platelets of the rabbit which have a fine oxyphile granulation

RÉSUMÉ

Le titre donné a notre symposium nous amene a y discuter d une part des éléments biochimiques reconnus qui jouent un role dans les *états d hypersensibilité* soit qu il s agisse d *allergie naturelle* soit d *anaphylaxie* expérimentale et reproductible d autre part des facteurs biochimiques qui interviennent lors des différentes reactions d hypersensibilite

1 Conditions d apparition de l hypersensibilite

S il existe de toute évidence une grande analogie fondamentale entre les différentes formes de sensibilisation anaphylactiques observées chez diverses especes animales nous ne trouvons pas de raison d admettre d identité absolue entre un état allergique naturel presque exclusivement observé chez l homme et un état similaire expérimentalement provoque Dans tous les cas l état anaphylactique semble etre causé par la présence d un anticorps précipitant spécifique pour l antigene sensibilisant mais dont la répartition dans le plasma sanguin et dans les tissus differe dans les trois especes animales selon qu il s agit de lapin de chien ou de cobaye chez lesquelles ce phénomene a été étudie très minutieusement

a) *Cobaye* Il existe selon nous de fortes raisons de penser que chez le cobaye une fixation predominante de précipitines dans les tissus provoque l état anaphylactique bien que des tentatives aient été faites recemment pour redonner vie à la theorie selon laquelle il y aurait une production d une « anaphylatoxine » provenant de l inter réaction de l antigène et de l anti corps dans le sang

b) *Chien* Chez le chien aussi la fixation d anticorps en particulier dans les cellules du foie a éte demontrée et semble bien etre la cause de l état anaphylactique Cependant un milieu sanguin normalement coagulable semble necessaire pour le déclenchement de la reaction de choc dans un organe en reponse a l administration de l antigene

c) *Lapin* Ce qu on appelle anaphylaxie chez le lapin est du par opposition a ce que l on observe chez les autres espèces animales à un anticorps circulant dans le sang qui à la suite d un contact soudain avec l antigène provoque une agglutination des plaquettes exceptionnellement nombreuses et riches en histamine chez cette espece animale

d) *Homme* Pour autant qu il soit possible de le savoir l allergie de l homme se rapproche davantage de l anaphylaxie du cobaye que de celle des deux autres especes animales étudiées

2 La réaction d hypersensibilité

Pour toutes les especes étudiées la cause directe de cette reaction semble etre la libération de substances pharmacodynamiques actives des cellules de type différent cellules musculaires lisses ou cellules directement

apparentees avec elles pour le cobaye cellules hepatiques pour le chien et plaquettes sanguines pour le lapin Parmi ces substances l histamine la premiere a ete reconnue en tant qu entite chimique elle reste une des substances dont l action sur les reactions allergiques ou anaphylactiques e t la plus certaine

La 5 hydroxytryptamine dont on a beaucoup parlé recemment en tant que constituant de nombreuses cellules est elle aussi libérée dans les memes conditions sans qu il soit possible d affirmer son role exact dans le domaine des reactions allergiques L heparine fait perdre au sang sa propriete de coagulation sa presence caracterise particulierement l état de choc anaphy lactique chez le chien

Une reaction allergique surtout dans son dernier stade présente encore d autres caracteres qu on ne peut attribuer raisonnablement aux substances que nous venons de nommer ils peuvent etre imputables a une ou plusieurs substances peptidiques liberees par des cellules lesees ou provenant du clivage proteolytique initie par ces lesions

Nous serons aussi amenés a penser que la liberation d histamine et d autres substances similaires peut induire la premiere phase d un tel pro cessus enzymatique

Il ne faut pas oublier cependant que l action de ces substances varie selon les especes animales et que les muridés par exemple sont peu sen sibles a l histamine

Nous devons aussi tenir compte du fait recemment demontre que les cellules « Mastocytes » d Ehrlich contiennent et peuvent liberer non seulement de l heparine (ce qui explique peut etre la coloration basophile metachromatique de leurs granules) mais aussi de l histamine Mais la encore il faut se garder de donner a la presence de cette substance une signification trop absolue il existe certainement dans l organisme d autres sources cellulaires d histamine comme par exemple les plaquettes sanguines chez le lapin qui contiennent de fines granulations oxyphiles

ZUSAMMENFASSUNG

Der fur unser Symposium gewahlte Titel veranlasst uns hier einerseits die gewonnenen biochemischen Erkenntnisse zu diskutieren die fur den Uberempfindlichkeitszustand sowohl der naturlichen Allergie als auch der experimentell erzeugten und reproduzierbaren Anaphylaxie eine Rolle spielen Andererseits wollen wir uber die biochemischen Faktoren bei den verschiedenen Typen der Überempfindlichkeitsreaktionen diskutieren

1 Bedingungen fur das Auftreten einer Überempfindlichkeit

Wenn aller Wahrscheinlichkeit nach auch eine grosse Basisubereinstim mung bei den verschiedenen Typen einer anaphylaktischen Sensibilisierung bei den verschiedenen Tierarten besteht so haben wir doch keinen Grund anzunehmen [illegible] tur liche Allergie [illegible] den ubereinstimm [illegible] and

durch die Anwesenheit eines prazipitierenden fur das sensibilisierende Antigen spezifischen Antikorpers bedingt zu sein dessen Verteilung im Blutplasma und in den fixierten Zellgeweben bei den 3 Tierarten — dem Kaninchen dem Hund dem Meerschweinchen — bei denen man dieses Phanomen genau studiert hat verschieden ist

a) *Meerschweinchen* Nach unserer Meinung spricht vieles dafur dass beim Meerschweinchen eine vorwiegende Fixierung des Prazipitins in den Geweben den anaphylaktischen Zustand hervorruft Man kann dies trotz der jungst aufgestellten Theorie annahmen nach der im Blut durch gegenseitige Einwirkung des Antigens und Des Antikorpers ein Anaphylotoxin produziert werden sollte

b) *Hund* Auch beim Hund weisen unsere Erkenntnisse darauf hin dass eine Antikorperfixierung an den Zellen besonders der Leber der Grund des Anaphylaxiezustandes zu sein scheint Indessen durfte in einer noch nicht genau bestimmten Weise die Beteiligung des normal gerinnbaren Blutes fur die volle Ausbildung der primaren Schockreaktion in diesem Organ notwendig sein

c) *Kaninchen* Bei den Kaninchen unterscheidet sich das unter dem Namen Anaphylaxie bekannte Phanomen von den vorhergehenden Beobachtungen Der anaphylaktische Zustand resultiert aus dem Zusammentreffen des im Blut zirkulieren den Antikorpers mit seinem Antigen was nach einer noch nicht bekannten Weise die Agglutination der Thrombozyten bewirkt welche bei dieser Tierart besonders zahlreich und reich an Histamin sind

d) *Mensch* Soweit man es beurteilen kann scheint die menschliche Allergie der Anaphylaxie des Meerscheinchens am ahnlichsten zu sein

2 Die Überempfindlichkeitsreaktion

Bei allen untersuchten Tierarten scheint das direkt auslosende Moment dieser Reaktion der Freisetzung von pharmakodynamisch wirksamen Substanzen aus den verschiedenen Zelltypen zu liegen den Muskel oder deren verwandten Zellen bei den Meerschweinchen den Leberzellen bei den Hunden und den Thrombozyten bei den Kaninchen Als erste dieser Substanzen wurde Histamin in seinem chemischen Wesen erkannt Histamin blieb auch bis heute das Agens dessen Einfluss auf allergische oder anaphylaktische Reaktionen am sichersten ist

Das 5 Hydroxy Tryptamin uber das als Bestandteil von vielen Zellen in letzter Zeit viel gesprochen wurde gehort auch zu den freigesetzten Substanzen es war aber bisher noch nicht moglich das Ausmass seiner Beteiligung bei allergischen Reaktionen genau zu bestimmen Das Heparin welches den Verlust der Blutgerinnungsfahigkeit verursacht charakterisiert durch seine Anwesenheit insbesonders den anaphylaktischen Schockzustand beim Hund

Eine allergische Reaktion besonders im letzten Stadium zeigt noch andere Merkmale fur die man die besprochenen Substanzen nicht verantwortlich machen kann Sie konnten moglicherweise einer oder mehreren peptischen Substanzen zugeschrieben werden die von den ladierten Zellen freigesetzt werden oder von der durch die Lasionen verursachten proteolytischen Aufspaltung herruhren

Wir konnten uns auch vorstellen dass die Freisetzung von Histamin und anderen gleichartigen Substanzen die ersten Stufen einer solchen Fermen reaktion bedingen konnte

Man darf indessen nicht vergessen dass sie Wirkung dieser Substanzen je nach der Tierart sehr variiert und die rattenahnlichen Tiere zum Beispiel nur gering auf die Histaminwirkung ansprechen

Wir mussen auch die kurzlich aufgezeigte Tatsache berucksichtigen dass die Ehrlichschen Mastzellen nicht nur Heparin enthalten und freisetzen konnen (was eventuell die basophile metachromatische Koloration ihrer Granula erklart) sondern auch Histamin Man soll sich indessen huten der Anwesenheit dieser Substanz zu grosse Bedeutung beizumessen es gibt im Organismus bestimmt noch andere Herkunftsmoglichkeiten zellu larer Art fur das Histamin wie zum Beispiel die Thrombozyten des Kanin chens die eine feine oxyphile Granulation haben

RESUMEN

El título dado a nuestro symposium nos autoriza a tratar por un lado la naturaleza de la *condicion* de hipersensibilidad ya sea *alergia* natural o *anafilaxia* experimental y por otro los factores bioquímicos de los diferentes tipos de *reaccion*

1 *La condicion de hipersensibilidad*

Aunque hay evidentemente una gran analogia entre los distintos tipos de sensibilisacion anafilactica en diferentes especies animales no debe suponerse que la condicion alérgica estudiada casi exclusivamente en el hombre se corresponde en todos sus detalles con ellos La anafilaxia parece deberse en todos los casos a la presencia de un anticuerpo precipitante específico para el antígeno en cuestión pero cuya distribución en el plasma y tejidos varia segun la especie

a) *Cobayo* Aunque recientemente se ha revivido la teoría de la formación de una «anafilatoxina», que aparecería como consecuencia de la reacción entre antigeno y anticuerpo en la sangre hay más argumentos en favor de una fijacion del anticuerpo en los tejidos

b) *Perro* Hay asimismo una fijación de los anticuerpos en las celulas en el hígado en especial aunque la participación de la sangre parece ser también necesaria para el shock

c) *Conejo* Lo que se llama anafilaxia en el conejo es debido al anticuerpo circulante en la sangre que luego de su unión con el antigeno produce una aglutinación de las plaquetas excepcionales en el conejo por su abun dancia y contenido en histamina

d) *Hombre* La alergia humana tiene más puntos de contacto con la anafilaxia en el cobayo que con las reacciones en otras especies

2 *La reaccion de hipersensibilidad*

En todos los casos la causa directa de la reaccion parece ser la liberación de una sustancia farmacológicamente activa Esta liberación la efectuan las células musculares en el cobayo las hepáticas en el perro las plaquetas en el conejo De las posibles sustancias la primera señalada y la que está más vinculada con el estado anafiláctico o alergico es la histamina La 5 hidroxi triptamina ha sido muy estudiada recientemente y es un cons

tituyente de muchas células pero su papel no es muy claro La heparina es responsable de la incoagulabilidad de la sangre especialmente característica en el *shock* en el perro *La reacción alérgica* sobre *todo en su* fase avanzada es producida también por otras sustancias de naturaleza peptídica formadas como consecuencia de las lesiones celulares Es muy posible que tanto la histamina como otras sustancias activas puedan ser liberadas por una acción enzimática Debe tenerse en cuenta sin embargo que una misma sustancia puede tener distinta acción en diferentes especies la histamina por ejemplo es casi inactiva en los múridos

Investigaciones recientes indican que los mastocitos de Ehrlich contienen y pueden liberar no solamente heparina sino también histamina En este caso asimismo debe cuidarse de no exagerar el significado de este hecho ciertamente hay otras células en el organismo que pueden producir histamina como las plaquetas del conejo que tienen una fina granulación oxífila

MECHANISM OF ANAPHYLAXIS

by

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The anaphylactic reaction of plain muscle can be considered as a sequence of reactions which starts with the union of antigen with cellular antibody and ends with muscular contraction This sequence can be interrupted at various points and the general plan of the present work has been to analyse the anaphylactic reaction by trying to inhibit its course (1 2 3) Inhibitors can act at three main stages they can interfere with the antigen antibody reaction or with the reactions which follow and which lead to the release of histamine and other active substances or with the effects of the released substances on the plain muscle cell

EFFECT OF ANTIHISTAMINES

It has long been recognized that antihistamines are much less active in antagonizing the anaphylactic contraction of plain muscle than the effects of histamine on the plain muscle (4 5) The reasons for this discrepancy are not fully understood but several factors probably contribute to it One of these is the release in addition to histamine of a slow reacting substance in anaphylaxis which is not antagonized by antihistamines (6 7) Slow reacting substance is released during the anaphylactic reaction of human and guinea pig lung but since it seems to contract only human and not guinea pig bronchi (8) it cannot provide a universal explanation of the failure of antihistamines

Another factor which is no doubt relevant to this failure is the high concentration of relea ed histamine when it reaches its site of action the plain muscle cell In this connection the role of mast cells (9) in anaphylaxis must be considered It seems well established now that mast cells plav an important part in the anaphylactic reaction of the guinea pig (10 11)

Since the histamine content and mast cell content of guinea pig lungs are correlated it seems reasonable to assume that much of the histamine released from guinea pig lung in anaphylaxis comes from the mast cell granules

Mast cells in the guinea pig are closely embedded between plain muscle cells and it can be imagined that the latter become bombarded by concentrated « packets » of histamine in the course of the anaphylactic reaction Since antihistamines are competitive antagonists whose effects can be overcome by high concentrations of agonist they would not be excepted to antagonize effectively the high concentrations of histamine encountered in the vicinity of mast cells For this reason their antagonism of the anaphylactic reaction of plain muscle is likely to be incomplete

It is worth considering whether another type of compound might be more effective

The preceding argument applies to the conventional competitive antihistamines but it is possible that an antihistamine which formed stable links with histamine receptors similar to those formed by dibenamine with adrenaline receptors would be more effective in the anaphylactic reaction of plain muscle The action of such a compound would be independent of the concentration of histamine and it might therefore be expected to antagonize histamine even in the vicinity of the source of release

CELLULAR BASIS OF ANAPHYLAXIS

A release of histamine by antigen from a sensitized tissue can only be obtained as long as the cell structure is intact (12 13) When sensitized guinea pig lung is sliced or chopped it retains the capacity to release histamine with antigen as long as the tissue slices are large enough to contain mainly intact cells but when the chopping is carried to the point where many individual cells become damaged the anaphylactic mechanism also becomes damaged and the amount of histamine released by antigen declines If tissue disintegration is carried to the point where all the cells are destroyed and only the intracellular particles remain intact histamine release by antigen ceases although the histamine releasers remain effective

The failure of isolated intracellular particles to release histamine is not due to their containing a special kind of histamine which is not released in anaphylaxis On the contrary it can be shown by experiments in which the antigen is applied to chopped lung and this is later homogenized that the intracellular particles have lost much of their histamine content The histamine containing intracellular particles in homogenates are probably mainly mast cell granules (14) and the question arises why the granules do not react with antigen when isolated although they do so *in situ*

This question cannot be satisfactorily answered largely because information is lacking about the location of antibody in the mast cell indeed it has not been shown yet that mast cells contain antibody at all Assuming that they do contain antibody this could be located on the surface or inside the cell If located on the surface it would be understandable that disruption of the cell structure also disrupts the reactions which lead to disintegration of the granules If antibody were located inside the cell for which there is a certain amount of evidence (15 16) it could perhaps be assumed that

some cofactor is lost during cell disintegration which is required to complete the reactions initiated by the antigen antibody union

Octylamine produces effects on mast cells which are entirely different from those produced in the anaphylactic reaction It produces a coalescence of the granules manifested by a uniform blue discoloration of the entire interior of the mast cell (11)

METHODS FOR STUDYING INHIBITION OF ANAPHYLAXIS

Inhibitors of the anaphylactic reaction can act at various sites and in order to distinguish between these sites two types of test are especially useful Tests of inhibition of histamine release distinguish between actions on the effector cells and actions on the histamine release mechanism and tests of desensitization distinguish between effects on the histamine release mechanism and effects on the antigen antibody reaction It was pointed out that sliced or chopped tissue can be used to test for histamine release in anaphylaxis provided that the cell structure remains intact The present experiments were carried out largely on chopped sensitized guinea pig lung A number of samples of uniform material in the shape of rods of about 0 5 mm cross section can be obtained from the same lung thus eliminating the factor of individual variation in the degree of sensitization Histamine assays can be performed with accuracy on the guinea pig ileum using automatic assay apparatus

EFFECTS OF METABOLIC INHIBITORS

Iodoacetate and cyanide inhibit histamine release by antigen but potentiate the effects of histamine releasers such as octylamine and compound 48/80 (1) This suggests that the anaphylactic reaction depends on an energy requiring mechanism The finding that iodoacetate and parachlormercuribenzoate both sulphydryl reagents inhibit the anaphylactic reaction in low concentrations may indicate that a reaction involving free sulphydryl groups forms an integral part of the anaphylactic reaction but no definite conclusions can be drawn as to the precise mode of action of metabolic inhibitors because their effects in living tissues are so widespread

A point of special interest is whether the anaphylactic reaction *per se* is an oxidative reaction as was first suggested by Parrot (17) It can be shown that oxygen lack acts like iodoacetate and cyanide in inhibiting histamine release in anaphylaxis and potentiating the histamine releasers but this does not necessarily prove that oxygen is required specifically for the anaphylactic reaction mechanism it may be simply that the latter requires a functioning cell More direct evidence for an oxidative mechanism is the demonstration that in the anaphylactic reaction of guinea pig lung a slight but significant increase in oxygen consumption occurs (18) which cannot be attributed to contraction of the plain muscle of the bronchioles since it is not produced by histamine

INHIBITION OF HISTAMINE RELEASE BY ANTIPYRETICS

All antipyretics so far tested inhibit histamine release in anaphylaxis Weak antipyretics such as salicylates are relatively weak inhibitors and strong antipyretics such as amidopyrine are strong inhibitors of histamine release (1) Phenyl butazone is particularly effective in inhibiting the anaphylactic reaction and this is interesting because of its clinical effectiveness in rheumatoid arthritis which is itself probably an allergic condition It is nevertheless doubtful that any of the drugs so far investigated can be considered as specific anti anaphylactic agents They all produce other inhibitory effects such as depression of oxygen consumption and depression of contractility of plain muscle in about the same concentrations in which they produce inhibition of histamine release by antigen and their anti anaphylactic effect may be only one of the manifestations of a general depression of cell function

ANALYSIS OF THE INHIBITORY ACTION OF PHENOL ON THE ANAPHYLACTIC MECHANISM

Phenol has antipyretic activity although it is too toxic for general use It is a very potent inhibitor of histamine release in anaphylaxis and since its effects are readily reversible its mechanism of action has been subjected to further analysis

Inhibitors can either block the release of active substances or their effects Phenol has some depressant effect on plain muscle but its main action lies in inhibiting histamine release It must be next enquired whether it interferes with the antigen antibody reaction or with a later process

There is no evidence that phenol interferes with the reaction of antigen with fixed antibody It neither inactivates antibody nor does it prevent desensitization If a sensitized guinea pig intestine is treated with antigen in the presence of phenol the anaphylactic contraction is inhibited but nevertheless if the phenol is later washed out the muscle is desensitized Similarly when sensitized lung is treated with antigen in the presence of phenol it fails to release histamine but if the phenol is then washed out it is desensitized

A feature of the inhibitory action of phenol is that it interrupts the anaphylactic reaction in such a way that the reaction cannot resume when the inhibitor is later removed The point is perhaps best explained by an analogy from a mechanism which behaves differently in relation to inhibitors The last stage of the reaction of fibrinogen with thrombin consist of an aggregation reaction which can be inhibited by ethylene glycol (19) [illegible] of ethylene [illegible] col [illegible] ved [illegible] from the system polymerization gets under way and clotting occurs If phenol acted like ethylene glycol in inhibiting the aggregation of the antigen

antibody complex it might be expected that after its removal the anaphylactic reaction would again get under way and histamine release would occur In fact there is no histamine release after removal of phenol under these conditions In order to explain this action of phenol a new hypothesis is required and the following enzymatic by pass mechanism has been suggested to account for it

It has been assumed that the combination of antigen with cellular antibody results in the activation of an enzyme system which catalyses reactions leading to histamine release An inhibitory substance such as phenol *might block the actions of this enzyme but not its transformation so that* after removal of the phenol no free enzyme would be left to complete the reaction

Further evidence of an enzymatic reaction in anaphylaxis is provided by the effects of temperature and pH

EFFECTS OF TEMPERATURE

The temperature curve of the histamine release reaction in anaphylaxis resembles an enzyme curve (2) It rises from zero at about 15° to a maximum at about 40° and then falls abruptly reaching zero at 44° 45° In a typical rate curve of an enzymic reaction the rise of the curve can be attributed to an increase in reaction rate and the fall to inactivation of the enzyme itself A similar explanation is likely to hold for the histamine release reaction It can be shown that low temperatures produce a reversible slowing and high temperatures (above 42 5°) an irreversible inactivation of the histamine release mechanism

The inactivation of the anaphylactic mechanism produced by raising the temperature can be demonstrated on sensitized guinea pig plain muscle If a sensitized uterus is heated to 45° for 5 minutes and then replaced in Ringer solution at 37° it fails to contract with antigen although it still contracts with histamine Similarly if sensitized guinea pig lung is heated to 45° for 5 minutes its capacity to release histamine with antigen is destroyed

These findings show that the anaphylactic reaction depends on a heat labile factor The nature of the heat labile factor has been investigated by the technique of passive sensitization *in vitro* This powerful technique which was first introduced by Dale (20) has been relatively little used although it presents no technical difficulties guinea pig tissues can be strongly sensitized *in vitro* in a few hours or less Experiments were *carried out in which (a) antibody which had been heated to 45° was* incubated with normal lung or intestine *in vitro* (*b*) normal antibody was incubated with lung or intestine which had been heated to [illegible] Method (*a*) gave normal sensitization whilst method (*b*) gave no sensitization showing that a factor present in normal tissue and required in the [illegible] hylactic reaction is destroyed at 45°

The rate of inactivation of the heat labile factor was measured [illegible] temperature coefficient determined The temperature coefficient [illegible] rise in temperature is 1 9 which corresponds to temperature [illegible] found in the inactivation of proteins It was concluded [illegible] labile factor is probably a protein

This assumption fits in with the previously discussed activation hypothesis since the heat labile protein may function as a proenzyme whose inactivation blocks further reaction steps

EFFECTS OF CALCIUM AND pH

The ionic requirements of the anaphylactic histamine release reaction are extraordinarily specific (3) Calcium appears to be the only cation required If calcium is omitted from Tyrode solution histamine release by antigen is greatly reduced and if a calcium chelating agent (EDTA) is also added histamine release is abolished Magnesium and potassium can be omitted without producing any effect and even sodium may be omitted and replaced by sucrose without inhibiting histamine release completely Calcium lack affects the anaphylactic mechanism selectively since histamine release by octylamine is not reduced and oxygen consumption is very little affected

The curve of histamine release in anaphylaxis in relation to pH also resembles an enzyme curve Maximum activity occurs at pH 7 8 and the reaction is almost completely inhibited at pH 6 3 The effects of calcium and pH are interdependent The inhibition of histamine release at pH 6 can be counteracted by increasing the concentration of calcium ten fold and conversely low calcium can be counteracted by making the pH more alkaline These findings suggest that the anaphylactic reaction requires bound calcium and that the binding decreases with pH It is unlikely that calcium is bound to carboxyl groups of a protein since this binding is not affected by pH in the experimental range but it is possible that calcium combines with an imidazole group since the nitrogen atom of the imidazole ring forms complexes with divalent cations which dissociate at about pH 6

CORRELATION BETWEEN EFFECTS OF INHIBITORS ON HISTAMINE RELEASE AND MAST CELL DEGRANULATION

The various agents which inhibit histamine release in anaphylaxis such as phenol iodoacetate calcium lack and raised temperatures also inhibit mast cell degranulation in anaphylaxis (11) Furthermore it can be shown that phenol inhibits mast cell degranulation without inhibiting desensitization just as it inhibits histamine release without inhibiting desensitization

These findings provide a concrete background for the enzymatic hypothesis if it is assumed that the lysis of mast cell granules in anaphylaxis is due to enzyme action The finding that phenol blocks degranulation but not desensitization indicates that a by pass mechanism exists as has been previously suggested

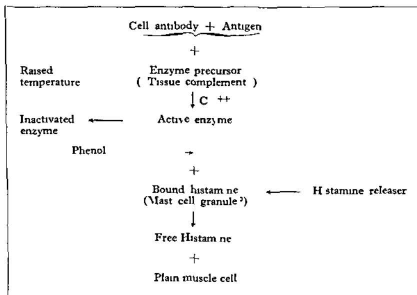
ANAPHYLACTIC REACTION AND COMPLEMENT REACTION

There are similarities between the anaphylactic reaction and the serum complement reaction Both depend on a heat labile factor both require

calcium and both are similarly affected by pH (21) The heat lability of the anaphylactic reaction is rather greater than that of complement which is inactivated at 52° Calcium is known to be required for the binding and activation of the first component of complement (22) and it is possible that it plays a somewhat similar role in the intracellular reaction mechanism which occurs in anaphylaxis

The anaphylactic reaction depends on a heat labile component which is probably a protein It might be assumed that the reaction of antigen with cellular antibody activates this component in the presence of calcium in a similar way to that in which the antigen antibody reaction *in vitro* activates the first component of complement

A possible reaction scheme which can account for the various features of the anaphylactic reaction in the guinea pig so far discussed including the actions of the inhibitors is shown below



The main features of this scheme are as follows The reaction of antigen with cellular antibody activates a short lived enzyme system which is responsible for histamine release and other manifestations of anaphylaxis Calcium is required for the activation of the system Heating to 45° destroys the enzyme precursor and thus blocks further reactions Phenol inhibits histamine release by inhibiting an enzymatic reaction responsible for release but it does not block the transformation of the enzyme system itself and hence allows desensitization to proceed normally The effect of calcium lack would be expected to be different from that of phenol since in the absence of calcium the by pass mechanism would not function It can in fact be shown that in the absence of calcium histamine release and desensitization are both inhibited

CONCLUSION

The proposed scheme should be regarded as a working hypothesis which will no doubt have to be modified in the light of further experience Although there is considerable evidence for an enzymatic reaction in anaphylaxis the evidence is only circumstantial and not so far based on the isolation of an enzyme or its reaction products The similarities which have been detected between the anaphylactic reaction and the serum complement reaction are striking and probably significant but an important difference is that the serum complement reaction occurs in solution whilst the anaphylactic reaction is intracellular and this makes an accurate study of the latter a difficult undertaking

SUMMARY

The object of this work has been to study the mechanism of the anaphylactic reaction by inhibiting it at various stages Histamine release in anaphylaxis can be inhibited by metabolic inhibitors such as iodoacetate and by antipyretic and antirheumatic substances such as salicylates amidopyrine and phenylbutazone Phenol is an effective inhibitor of histamine release and it has been shown that it blocks histamine release without blocking desensitization It is suggested that combination of antigen with cellular antibody activates a short lived enzyme system which is required for the anaphylactic reaction In the presence of inhibitors such as phenol the enzyme system presumably becomes both activated and again inactivated so that when the phenol is removed no free enzyme is left to complete the reaction Evidence for the activation of an enzyme system is also provided by the effects of temperature and pH The anaphylactic mechanism operates only in a narrow temperature range It is reversibly inactivated at lower temperatures and irreversibly inactivated at temperatures above 43 45° Of the cations present in Ringer solution only calcium seems to be essential There is some evidence that calcium acts as an activator of the intracellular enzyme system in anaphylaxis and thus plays a somewhat similar role to that which it plays in the serum complement reaction

RÉSUMÉ

Ce rapport a pour objet l étude de la réaction anaphylactique par son inhibition expérimentale provoquee à ses stades divers

Dans l anaphylaxie la libération d histamine peut etre empechee par des agents inhibiteurs tels que l iodo acétate et des produits antirhumatismaux et antipyrétiques tels que les salicylates l amidopyrine et le phénylbutazone

Le phénol est un agent inhibiteur a action efficace sur la liberation d histamine et il bloque cette libération sans empecher la désensibilisation en cours

Il est suggere qu une combinai on entre l antigene et l anticorps cellulaire donne lieu à une entrée en action de courte durce d un systeme d enzymes facteur nécessaire a la production de la reaction anaphylactique En presence d agents inhibiteurs comme le phenol on peut supposer que le systeme d enzymes est tour a tour d abord active puis neutralise de telle sorte que lorsque le phénol est supprime il ne reste plus d enzymes libres pour que s acheve la réaction

De données probantes de l activation d un systeme d enzymes verifiees par l étude de la température et du pH sont présentées

Les degrés de temperature entre lesquels le mecanisme anaphylactique peut fonctionner sont etroitement délimités

Son activite peut etre neutralisee passagerement aux temperatures relativement basses et définitivement aux températures supérieures a 43 45°

Parmi les cations que contient la solution de Ringer seul le calcium semble jouer un role essentiel Certaines observations indiquent que le calcium a une action activante sur le système d enzymes intracellulaires dans l anaphylaxie et qu il joue ainsi un role quelque peu semblable a celui qu il a dans la reaction complémentaire du sérum

ZUSAMMENFASSUNG

Diesem Beitrag liegt das Studiem der anaphylaktischen Reaktion durch Beobachtung der in den verschiedenen Stadien experimentell ausgelosten Hemmungsphanome zugrunde

Bei der Anaphylaxie kann die Histaminfreisetzung durch verschiedene Hemmsubstanzen verhindert werden wie mit Jodazetat antirheumatischen Substanzen und antipyretischen Stoffen wie Salicylaten Amidopyrin und Phenolbutazon

Das Phenol ist eine Hemmsubstanz die wirksam die Histaminfreisetzung beeinflusst und es blockiert diese Freisetzung ohne die laufende Desensibilisierung zu blockieren

Es wird vermutet dass die Verbindung des Antigens mit dem zellularen Antikorper eine kurzdauernde Aktion eines Ferment systems notwendiger Faktor fur die anaphylaktische Reaktion veranlasst Man kann sich vorstellen dass bei Anwesenheit einer Hemmsubstanz wie des Phenols das Fermentsystem anfangs aktiviert dann neutralisiert wird und zwar in folgender Weise dass bei Entfernung des Phenols kein freies Ferment zur Auslosung der Reaktion mehr vorhanden ist

Beweisende Daten fur eine Aktivierung eines Ferment Sy tems werden ahnand von Temperatur und pH Studien vorgebracht

Die Temperaturen bei denen die Anaphylaxiereaktion vor sich gehen kann sind eng begrenzt

Seine Akt [illegible]
und durch h [illegible]

Unter der [illegible]
scheint nur [illegible]
tungen zeig [illegible]
zellulare Fermentsystem bei der Anaphylaxie spielt und dass diese Rolle derjenigen in der Serumkomplementraektion ahnlich ist

RESUMEN

El objeto del presente trabajo es el estudio del mecanismo de la reacción anafiláctica mediante su inhibición en distintas fa es del mismo La libe racion de histamina puede ser inhibida por varios inhibidores metabólicos como el iodoacetato o por sustancias antipireticas y antirreumáticas como los salicilatos amidopirina y fenilbutazona El fenol es un inhibidor potente de le liberación de histamina y se ha demostrado que actua sin impedir la desensibilizacion Se sugiere que la combinación del antigeno con el anticuerpo celular activa un sistema enzimatico efímero nece ario para la reaccion anafilactica En presencia de inhibidores como el fenol probable mente el sistema enzimático es inactivado luego de su activación inicial de tal modo que la cantidad de enzima remanente es insuficiente para completar la reacción

La influencia del pH y de la temperatura constituyen un aporte en favor de la existencia de un sistema enzimatico el mecanismo anafiláctico funciona solamente en un pequeno margen de temperatura siendo inactivado rever siblemente a baja temperatura e irreversiblemente por encima de 43 45° C De los cationes que contiene la solución Ringer sólo el calcio parece esencial probablemente actua como activador del sistema enzimático intracelular en la anafilaxia con un papel semejante al que desempeña frente al comple mento

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HISTAMINE AND OTHER MEDIATORS IN HYPERSENSITIVITY REACTIONS

by

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No one today would ascribe all the effects observed in anaphylaxis to histamine alone. Nevertheless opinions differ widely regarding the relative importance of histamine and diverge even further on the question of what other substances are involved, and indeed if certain effects are attributable to humoral substances at all. I cannot hope to discuss all the aspects of this question but shall endeavour to present evidence and arguement sufficient to permit a rational evaluation of the importance of various known substances.

It is reasonable to assume that one of the earliest results of the union of antigen with antibody is a rather specialized form of damage to the tissue and that this leads to the activation of enzymes and the freeing or formation of substances having pharmacological activity. Hence it is to be expected that different tissues will suffer varying degrees of primary damage [illegible]

well suffer damage but we have not yet discovered how to demonstrate it histologically. Secondary effects such as the occurrence of active pharmacological agents will similarly vary with the tissue depending upon the presence of active substances in a found form or substrates which can give rise to active substances, as well as the requisite enzymes or other mechanism for making them active.

As an illustration of the differences due to tissues Table I shows the amounts and types of gut contracting activity released by the antigen from particles of various blood free organs of the same guinea pig

TABLE I

Gut contracting substances which diffuse out of particles of various blood free tissues taken from the same sensitized guinea pig when the tissue is suspended in Tyrode solution containing the antigen

	HISTAMINE IN MUG/GRAM	SRS A IN UNITS	OTHER SUBSTANCES
Lung	7 000	300	Nil
Aorta or Vena Cava	800	45	Nil
Uterus	200	20	?
Trachea	500	trace	Nil
Skin	30	?	+
Pancreas	250	10	+
Cerebral hemisphere	Nil	Nil	Nil
Skeletal muscle	Nil	Nil	Nil
Liver	Nil	Nil	Nil

Apart from differences in the active substances formed the observed response will be decided by what types of reactive tissue are within range of these substances and here such factors as rate of destruction or inactivation diffusibility and the proximity of the site of action to the site of release must be operative

As an illustration of the difference in response which may be expected from the same organ from different species or even from closely related tissues of the same species Table II shows the comparative pharmacology of smooth muscle from the trachea or bronchioles of several species

There are yet further complications The antigen antibody reaction

TABLE II

The minimum effective concentrations of drugs on isolated bronchial muscle expressed as μg of base per ml

	BRONCHIOLES			TRACHEA		
	5 HT	HISTAMINE	ACh	5 HT	HISTAMINE	ACh
Cat	0.01	2.0	0.1	0.02	> 20	0.05
Rat	0.01	usually > 5	0.04	0.1	> 5	0.04
Dog	0.05	0.3	0.1	0.05	0.3	0.1
Guinea pig	0.4	0.4	0.4	0.4	0.4	0.4
Rabbit	> 8	0.5	0.2	> 8	> 5R	0.4
Rhesus monkey	> 20R	0.5	0.1	0.02	0.5	0.01
Man	> 20R	0.2	0.1	—	—	—

R denotes relaxation in the case of human bronchiole and rabbit trachea and a reduction in the response to ACh when 5 HT and ACh are applied simultaneously to the monkey bronchiole

can give rise to an immediate or a delayed response the reason being obscure but the mechanism undoubtedly being different in the two cases It is also becoming clear that the hormone balance of the animal can greatly modify tissue reactions and may therefore influence different antigen anti body reactions to a varying degree

The sum of these considerations leads to the conclusion that an exact replication of the response to the antigen antibody reaction can only be expected if the tissues are from the same organ of the same species and if the animals were under a comparable state of hormonal control and had a similar type and intensity of sensitization

I have introduced my subject in this way because I believe that clinicians generally are not interested in what goes on in the guinea pig or rat unless there is reason to suppose that it also occurs in man Furthermore whilst there may be certain points of similarity between the reactions primarily involving skin blood vessels nasal mucous membrane lung etc the details of the reaction and the various therapeutic problems which arise from these may be quite different

Thanks to the excellent antagonist drugs now available I believe that histamine is no longer the most important therapeutic problem and that

Thus

so that

Histamine

In 1929 Dale (1) said We may picture the anaphylactic shock (there fore) as the result of cellular injury Whether this is general or localized in a particular organ histamine will be released and its effects will be prominent in the resulting reaction imposing a general resem blance to the syndrome produced by histamine itself on the symptoms seen in each species As a general statement that histamine is released in anaphylaxis this cannot be disputed Where anomalies exist they can usually be attributed either to the rapid release of histamine at particular sites during anaphylaxis in a manner which cannot be satisfactorily paral leled by injection or other form of administration or alternatively to the tissue being relatively unresponsive to histamine compared with its sensi tivity to other substances which are now known or believed to occur The variation in the therapeutic usefulness of antihistamine substances in different conditions provides some degree of analysis for any particular allergic state In urticaria the amounts of histamine and the sites at which it acts are such that the antihistaminic drug can reach the site in an ade quate concentration Since this therapy is successful substances other than histamine cannot contribute seriously to the condition In the rat a comparable condition (passive cutaneous anaphylaxis) is normally accom panied by histamine release but in this species doses of antihistamine drugs coupled with pretreatment of the animal to reduce the histamine present in the skin to 10 p 100 of normal do not influence the reaction (2) In this case therefore although histamine is released it contributes little to the observed response this being due either to direct damage or to the participation of other active substances

Few anaphylactic states permit such clear conclusions regarding histamine Let us consider the case of asthma Only certain types of early case derive any material benefit from antihistamine drugs alone and many cases do not seem to be affected at all Yet we know that human asthmatic lung releases large amounts of histamine (3 4) and that histamine causes severe spasm of the smooth muscle of the bronchioles Even *in vitro* however where it is possible to employ antagonist substances at concentrations well above those practicable in therapy, the smooth muscle contraction produced when the specific antigen is applied to asthmatic bronchioles cannot be greatly diminished (3) This suggests that in this case also other substances are involved, or that the response is a direct result of the union of antigen with antibody However this tissue contains large amounts of histamine and although we know that large amounts are released we do not know exactly where this occurs or what concentrations are reached locally It is therefore possible that in severe asthma histamine is released locally in quantities too great for the antagonist drugs to block completely

In the particular case of human asthma a slow reacting substance (SRS A) now appears to be responsible for part of the bronchospasm previously attributed to histamine (4) so that both substances must be suppressed before the bronchospasm can be overcome This example therefore illustrates that even in conditions which do not appear to benefit significantly from anti histamine treatment histamine may still be important

Heparin

It is highly probable that heparin chondroitin sulphate or some similar substance is freed from mast cells whenever histamine is released from them In some species notably the dog the resulting increase in the clotting time of the blood is a feature of anaphylaxis Heparin causes no untoward effects and in some cases at least its release may be beneficial in preventing extravascular clotting of plasma proteins which have leaked out of the capillaries and by reducing the tendency for damaged cells of the vascular endothelium to collect platelets and leucocytes The latter effect has been demonstrated by Lecomte and Hughes (5) on the Arthus reaction in the mesentery of the rabbit The platelets and leucocytes of this animal are rich in substances having pharmacological activity and the blood is regarded as the major shock organ in this species so that heparin release may well reduce the severity of damage and symptoms in anaphylaxis In other species heparin may have a similar but much less important action

Acetylcholine

This substance has long been an unknown quantity in anaphylaxis Those who believe it to be important cite the beneficial effects of atropine and related substances and the adverse effects of anti cholinesterases on bronchospasm and glandular secretion Both glandular activity and normal bronchial tone are controlled by cholinergic nerves and atropine will therefore suppress these even in the absence of anaphylaxis The stress of dyspnœa in asthma may well increase vagal activity and atropine would

then be beneficial but no objective information is available Excessive viscid secretions in the bronchioles undoubtedly contribute to the embarrassment of ventilation in asthma although acetylcholine might be the active agent other substances such as bradykinin might equally well be involved since bradykinin is known to raise the rate of secretion of salivary glands even in the presence of atropine (6) The bronchospasm of anaphylaxis *in vivo* would be somewhat reduced by atropine even if acetylcholine played no part because the contraction would start from a lower level of resting tonus and atropine is known to cause a non specific depression of the response of certain smooth muscle organs to histamine and many other substances

In experiments upon the mechanism by which active substances were released during anaphylaxis from perfused guineapig lung I used di isopropylfluoro phosphonate to inhibit various enzymes which might have been acting Even in the maximum practicable concentration this inhibitor reduced but did not abolish the yield of active substances and when present only during the period before the addition of antigen it modified the time course of release but not the total output of histamine and SRS A (12) Pretreatment of the lung with DFP will destroy all cholinesterase activity and any acetylcholine resulting from the antigen antibody reaction should then be detectable in the perfusion fluid leaving the tissue When such perfusates were tested on the eserinized dorsal muscle of the leech no acetylcholine was found although small amounts of acetylcholine added to the fluid entering the lungs were detected quantitatively in the outflow showing that no destruction had occurred during passage through the organ Table III shows the amounts of histamine and SRS A released and the upper limit of acetylcholine which could have escaped detection in these experiments It is clear that under the conditions of the experiment acetylcholine is not released in quantities sufficient to contribute to the symptoms of anaphylaxis and furthermore that acetylcholine is not responsible for the release of histamine as has been postulated by Danielopolu (7)

TABLE III

Active substances present in fresh samples of effluent from perfused guinea pig lungs submitted to anaphylaxis *in vitro* after treatment with D F P 2×10^{-3} g/ml for 10 minutes

Assay for ACh performed on eserinized leech muscle very shortly after collection
Histamine and SRS A assayed on guinea pig ileum

SAMPLE	HISTAMINE µg/ml	SR A units/ml	ACh µg ml
1	1 2	60	0 002
2	0 7	80	
3	0 55	20	
4	0 25	18	
5	0 14	16	

Controls (i) 0 005 µg ACh added to 1 ml sample 1 and treated exactly as other samples gave biological response equivalent to ACh 0 005 µg/ml

(ii) ACh 0 2 µg slowly added to inflow to perfused lung after collection of samples and 40 mls effluent collected during 10 minutes Effluent should contain 0 005 µg/ml assay value = 0 007 µg/ml

A duplicate experiment gave similar results

5 hydroxytryptamine

This substance is present in the platelets of all species examined but the amount varies greatly with the species reviewed by Levy (8) Man and the guinea pig have relatively little whereas the rabbit has 30 times as much Humphrey and Jacques (9) have shown that 5 HT is released from platelets *in vitro* under conditions which would seem to resemble those existing during anaphylaxis *in vivo* If such a release occurs in human anaphylaxis it is doubtful if 5 HT contributes to the observed symptoms because destruction takes place at a high rate in the bloodstream when 5 HT is continuously infused in man (10) and also because when destruction is prevented by 5 hydroxytryptophane the accumulated 5 HT produces severe diarrhœa whereas no dyspnœa either of bronchomotor or vasomotor origin occurred (11)

It is clearly possible that the effects produced by substances in the bloodstream may bear little resemblance to those produced by local application to particular tissues Herxheimer (13) found that inhalation of an aerosol of a buffered solution of 5 HT produced little effect in man although it caused bronchospasm in guinea pigs This agrees with the results obtained with isolated bronchioles (Table II) which show that 5 HT does not constrict human bronchioles and that large doses actually relax them whereas bronchioles from various other species notably the cat contract vigorously to quite low concentrations

I have found that active shock perfusate from guinea pig lungs had no effect on the rat s uterus and therefore did not contain any significant amount of 5 HT although large amounts of histamine and SRS A were present This result corresponds with Herxheimer s observation (14) that antagonists to 5 HT failed to protect sensitized guinea pigs submitted to an aerosol of antigen as assessed by his micro shock method

There is thus no evidence that 5 HT plays any part in anaphylactic reaction in the lung of man or the guinea pig The muscle of human bronchioles does not respond to it (although by analogy with the Rhesus monkey that of the trachea might) and none has been found in the effluent perfusate from shocked lung although histamine and SRS A were present

In other sites and other species however 5 HT may play a part in anaphylaxis Fink (15) has reported that anaphylactic contraction of the sensitized uterus of the mouse can be abolished by LSD (*) When I performed comparable experiments using the uterus of the passively sensitized rat I was surprised to find (16) that whilst the response to 5 HT was reduced by a factor of 400 by the antagonist LSD the response to the

(*) Lysergic acid diethylamide

antigen was apparently unchanged Furthermore no tachyphylaxis to 5 HT was seen after the anaphylactic response as would be expected if 5 HT had been present in the tissue during the period of contact with the antigen 5 HT is more active than any other substance in producing œdema in the skin of the rat (17 18) However Inderbitzen and Craps (19) found that the œdema resulting from passive cutaneous anaphylaxis in the rat was not reduced when the animal was treated with maximal doses of both antihistamine and anti 5 HT drugs (which reduced the effect of intradermal 5 HT by a factor of 1 000) although the reaction caused some loss of both histamine and 5 HT from the skin Humphrey and I (20) obtained somewhat similar results when in addition the histamine and 5 HT content of the skin was depleted by treating the animals with courses of compound 48/80 and reserpine It seems that 5 HT does contribute to anaphylactic reactions in the skin of the rat but it represents only one of at least 3 mechanisms each able to cause the observed increase of capillary permeability However 5 HT could not play a comparable role in man because when injected intradermally into human skin it produces vasoconstriction (21) The participation of 5 HT in the anaphylactic contraction of smooth muscle organs such as the ileum which contains a considerable amount and the uterus which responds to low concentrations has not as yet been adequately studied

Bradykinin

When beta globulin from most species is digested by trypsin bradykinin is formed (22 23) Other enzymes (e g venoms) can act similarly and simple contact between plasma and glass leads to the formation of polypeptides having similar properties (24) The various similar products are now grouped under the title plasma kinins (25) The results which I shall mention have been obtained with or related to bradykinin itself Beraldo (26) reported that shortly after the onset of anaphylactic shock in the dog a substance which resembled bradykinin was detectable in the blood The amount was small and was not considered to contribute significantly to the symptoms of anaphylaxis There is no evidence regarding other species Anaphylactic shock in perfused isolated lungs of the guinea pig does not cause the appearance of detectable amounts of bradykinin nor was any found in comparable experiments with human lung (12) Although the smooth muscle of the gut and uterus of many species contracts to bradykinin that of the bronchial tree does not respond even to large doses whilst that of the vascular system relaxes

Increased capillary permeability results from intradermal injections of [illegible]

for human skin contains protease (29) which could be activated either as a direct consequence of the union of antigen with antibody or indirectly as a result of mild damage to the dermis Similarly damage to the capillaries would permit the escape of plasma proteins and thus create favourable

Controls (i) 0 005 µg ACh added to 1 ml sample 1 and treated exactly as other samples gave biological response equivalent to ACh 0 005 µg/ml

(ii) ACh 0 2 µg slowly added to inflow to perfused lung after collection of samples and 40 mls effluent collected during 10 minutes Effluent should contain 0 005 µg/ml assay value = 0 007 µg/ml

A duplicate experiment gave similar results

5 hydroxytryptamine

This substance is present in the platelets of all species examined but the amount varies greatly with the species reviewed by Levy (8) Man and the guinea pig have relatively little whereas the rabbit has 30 times as much Humphrey and Jacques (9) have shown that 5 HT is released from platelets *in vitro* under conditions which would seem to resemble those existing during anaphylaxis *in vivo* If such a release occurs in human anaphylaxis it is doubtful if 5 HT contributes to the observed symptoms because destruction takes place at a high rate in the bloodstream when 5 HT is continuously infused in man (10) and also because when destruction is prevented by 5 hydroxytryptophane the accumulated 5 HT produces severe diarrhœa whereas no dyspnœa either of bronchomotor or vasomotor origin occurred (11)

It is clearly possible that the effects produced by substances in the bloodstream may bear little resemblance to those produced by local application to particular tissues Herxheimer (13) found that inhalation of an aerosol of a buffered solution of 5 HT produced little effect in man although it caused bronchospasm in guinea pigs This agrees with the results obtained with isolated bronchioles (Table II) which show that 5 HT does not constrict human bronchioles and that large doses actually relax them whereas bronchioles from various other species notably the cat contract vigorously to quite low concentrations

I have found that active shock perfusate from guinea pig lungs had no effect on the rat s uterus, and therefore did not contain any significant amount of 5 HT although large amounts of histamine and SRS A were present This result corresponds with Herxheimer s observation (14) that antagonists to 5 HT failed to protect sensitized guinea pigs submitted to an aerosol of antigen as assessed by his micro shock method

There is thus no evidence that 5 HT plays any part in anaphylactic reaction in the lung of man or the guinea pig The muscle of human bronchioles does not respond to it (although by analogy with the Rhesus monkey that of the trachea might) and none has been found in the effluent perfusate from shocked lung although histamine and SRS A were present

In other sites and other species, however 5 HT may play a part in anaphylaxis Fink (15) has reported that anaphylactic contraction of the sensitized uterus of the mouse can be abolished by LSD (*) When I performed comparable experiments using the uterus of the passively sensitized rat I was surprised to find (16) that whilst the response to 5 HT was reduced by a factor of 400 by the antagonist LSD the response to the

(*) Lysergic acid diethylamide

antigen was apparently unchanged Furthermore no tachyphylaxis to 5 HT was seen after the anaphylactic response as would be expected if 5 HT had been present in the tissue during the period of contact with the antigen 5 HT is more active than any other substance in producing œdema in the skin of the rat (17 18) However Inderbitzen and Craps (19) found that the œdema resulting from passive cutaneous anaphylaxis in the rat was not reduced when the animal was treated with maximal doses of both antihistamine and anti 5 HT drugs (which reduced the effect of intradermal 5 HT by a factor of 1 000) although the reaction caused some loss of both histamine and 5 HT from the skin Humphrey and I (20) obtained somewhat similar results when in addition the histamine and 5 HT content of the skin was depleted by treating the animals with courses of compound 48/80 and reserpine It seems that 5 HT does contribute to anaphylactic reactions in the skin of the rat but it represents only one of at least 3 mechanisms each able to cause the observed increase of capillary permeability However 5 HT could not play a comparable role in man because when injected intradermally into human skin it produces vasoconstriction (21) The participation of 5 HT in the anaphylactic contraction of smooth muscle organs such as the ileum which contains a considerable amount and the uterus which responds to low concentrations has not as yet been adequately studied

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Increased capillary permeability results from intradermal injections of [illegible]

would permit the escape of plasma proteins and thus create favourable

conditions for local proteolytic activity during subsequent stages of the reaction

Although the isolated blood free lung does not form bradykinin during anaphylaxis and although this substance does not seem to contribute to bronchospasm it may nevertheless play some part *in vivo* Some degree of damage in the lung tissue and an increase of permeability of the capillaries may well result from the antigen antibody reaction either directly or by the action of histamine and other substances A situation similar to that postulated for the skin might then exist, for the lung is very rich in proteases (30) Any bradykinin formed here would presumably lead to œdema, particularly in loose connective tissue and to an increase in the secretions of the bronchial glands both effects being established clinical findings in prolonged anaphylactic states

Permeability factors

Substances such as α and β globulins of plasma — G_2 fraction (31, 32) and leucotaxine (33, 34 35) have never been proved to play any part in antigen antibody reactions because methods of proof have not yet been developed Nevertheless conditions favourable for these substances almost certainly occur in tissue and the kind of effect which these substances can produce fits readily into the clinical picture particularly that of skin reactions

Any increase in capillary permeability whether resulting from direct damage or histamine release would permit the escape of plasma globulins and thus prolong the condition The situation would be very similar to that which has been suggested for bradykinin and might occur in any tissue the duration of the effect of G_2 α-globulin would be governed by the ability of the tissue enzymes to destroy it

If cells suffer moderately severe damage the cathepsins will escape and these enzymes would vary in type with the kind of cell from which they came and thus with the site of the reaction Outside the cell these enzymes have various proteolytic actions and would presumably attack the damaged cells from which they came and adjacent tissue, thus forming leucotaxine—a name given to a group of peptides which contain about 14 amino acids Leucotaxine increases capillary permeability and by chemotaxic attraction causes leucocytes to leave the capillaries and accumulate in the tissue Its formation would depend upon tissue damage of moderate severity or particular type and would not be immediate This delay, and its properties would suggest a role for leucotaxine in the tuberculin reaction, allergic eczemas and periarteritis

SRS A

This substance has been the main subject of my research during the last seven years It is formed in the perfused tissue when sensitized lung of man monkey guinea pig or rabbit is challenged by the specific antigen and is found together with histamine in the effluent perfusion fluid The routine test object is the guinea pig s ileum treated with a high concentration of an antihistamine drug, to block the effect of histamine and reveal that of SRS A (4)

The existence of this substance was reported in 1940 (36) but until the introduction of specific antihistamine drugs detailed study was not practicable It has now been found that of the few smooth muscle preparations which are caused to contract by SRS A one is human bronchial muscle so that the existence of this substance has obvious implications in clinical medicine

SRS A comes from the lung tissue itself as a result of the antigen antibody reaction This has been shown by the following experiments (i) cleanly perfused lung gives yields of SRS A which are as large as those from lung which still contains some blood Furthermore the addition of normal serum does not increase the yield (ii) If the lungs are taken from animals which have been treated with antiserum to destroy their platelets a considerable yield of SRS A is still obtained (iii) When the effluent perfusate is tested within 30 seconds of leaving the lung the SRS A is already present and no further activity develops on storage

has been washed out of this tissue by the perfusion fluid (12) SRS A must therefore be formed or converted into an active form by the anaphylactic reaction and thus differs from histamine which is freed from a pre existing store This difference in mechanism of release from the lung is suggested by the time course of appearance of the two substances in the shock perfusate Table IV refers to the results obtained with perfused human asthmatic lung challenged *in vitro* by one of the major antigens Experiments with guinea pigs gave substantially the same picture

TABLE IV

Assay on the atropinized guinea pig ileum of samples of effluent collected from a perfused segment of human asthmatic lung (about 200 g) before and after the addition of antigen (birch pollen) to the perfusion fluid

ASSAY	BEFORE ANTIGEN	AFTER ANTIGEN — TIME IN MINUTES				
		0 1	2 4	5 0	1 28	29 31
Total gut contracting activity per minute expressed as µg histamine	Nil	0 5	30	9	5	2
Percentage of activity (*) which remains when the response to histamine is abolished (**)	Nil	?	14	40	50	70

( ) The t v ty w s c mp red t the l v l of spon obta ned w th hi tam n 10 g/ml before add ng mepyramine
( ) M pyram ne (neoa tergan pyrilam n) 10⁻⁴ g ml

Whereas histamine is freed suddenly in a great flood and thereafter falls off rapidly SRS A release begins concurrently with or very shortly after that of histamine and has no early explosive component The maximum rate of release is rapidly reached and thereafter the rate decreases gradually during 30 minutes or longer Such a time course of SRS A output would be expected if the mechanism by which it was formed was activated very rapidly as a result of the antigen antibody union and there after became inactivated slowly possibly with some concurrent reduction in the amount of substrate available

SRS A is not released from perfused lung by histamine or acetylcholine neither is its release during anaphylaxis influenced by antihistamine drugs there is therefore no reason to suppose that it occurs either as a conse quence of histamine release or as the result or vagal activity

The source of the SRS A used in all the experiments on its pharmacology has been the guinea pig lung Human asthmatic lung is too scarce to permit more than a few experiments with human SRS A but fortunately guinea pig SRS A appears to be the same substance (4) When active perfusate from the two species is purified by the same charcoal method losses of the same order are sustained the purified products migrate electrophoretically in parallel fashion although with heavy loss of activity in each case Charcoal purified SRS A from the two species causes contractions of the guinea pig ileum which are identical in profile and show the same dose response relationship both products also cause contraction of normal human bronchioles *in vitro* It is therefore believed that the two species produce SRS A having the same or very closely similar pro perties

Although lung from both man and the guinea pig produce SRS A during anaphylaxis the isolated bronchioles from the two species have a quite different order of sensitivity to it Guinea pig bronchioles and trachea *in vitro* have failed to show any response to SRS A in a concentration 4 to 10 times that which contracts human bronchioles although all the prepa rations contract to similar concentrations of histamine or acetylcholine If these tissues behave in this way *in vivo* it follows that SRS A contributes much less to the anaphylactic bronchospasm of the guinea pig than it does during asthma in man this could account for the different degree of pro *tection which the antihistaminic drugs can exert in the two species* Since SRS A has a very prolonged action and does not appear to produce tachy phylaxis it has the requisite properties for producing *status asthmaticus* Only man will behave in this way since the bronchioles of the guinea pig and even of the Rhesus monkey are much less reactive to SRS A

From a consideration of the relative potencies of histamine and SRS A on the guinea pig ileum and human bronchioles and the assay values of the active perfusate from human asthmatic lung some idea can be obtained of the relative contribution which each substance makes to the broncho spasm in human asthma Table IV shows that when fractions of perfusate collected during various periods are assayed on the gut 14 p 100 40 p 100 50 p 100 and 70 p 100 respectively of the total activity is attribu table to SRS A The effective dose levels for human bronchioles differ from those for the guineapig gut being about 3 times greater in the case of SRS A and at least 10 times greater in the case of histamine Therefore

—ignoring the differences in dose response relationship—the percentage of the total effect of human shock perfusate on human bronchioles which would be attributable to SRS A would be 33 p 100 66 p 100 75 p 100 and 87 p 100 in the various samples I quote these very approximate figures simply to show that SRS A is not merely a curiosity but probably is capable of producing a serious broncho constriction even when the effects of histamine are eliminated Schild *et al* (3) who studied isolated bronchioles from asthmatic patients found that more than 70 p 100 of the anaphylactic contraction could not be prevented by very high concentrations of an antihistamine drug This mepyramine resistant contraction can now be explained as due to SRS A the effect of which was unmasked when that of histamine had been abolished SRS A is a highly active acidic substance the purest samples being effective on the guinea pig ileum at a concentration of 1 μg/ml Purification is difficult and even samples which had been submitted to electrophoresis as the final stage of separation gave infra red absorption spectra which showed that impurities were still present The absorption spectra therefore provide only limited information the most active sample was predominantly carbohydrate and there was no evidence for the presence of either phosphorous or amino acids although small amounts could have been masked

Samples of sufficient size and purity to be tested in man have not yet been obtained I do not know therefore whether SRS A can produce any effects other than bronchospasm

Antagonist drugs have been tried against SRS A using the cavy ileum as test object Significant reduction of the response to SRS A was caused by an increase in the calcium concentration of the bath fluid and also by atropine 10 g/ml isoprenaline 10^{-7} g/ml adrenaline 10^{-8} g/ml theophylline 10^{-8} g/ml and then on ionic detergent Triton W R 1336 10^{-} g/ml None of these substances acts specifically against SRS A since the response of the cavy ileum to other active substances was depressed also The effect of calcium was noticeable when the concentration was raised from 4 to 5 milli equivalents per litre and at 8 milli equivalents per litre the contraction was reduced by 50 p 100 This observation would appear to offer a rational explanation for the inclusion of calcium with anti histamine solutions for inhalation in the treatment of asthma W R 1336 is a wetting agent used as an aerosol in the cold steam treatment of bronchial congestion It has been thought to act by liquifying the secretions but since it inhibits sustained contractions of the ileum it may also relax bronchial muscle in a non specific manner Atropine has a similar effect on human bronchial rings to that observed on the ileum

Anaphylaxis can be totally suppressed by the removal of all calcium ions neither histamine nor SRS A is then released from sensitized lung by the antigen If the tissue is perfused with solution containing D F P at maximum solubility (approx 2×10^{-3} g/ml before and during the addition of antigen the yields of both histamine and SRS A are reduced to about 20 p 100 of the control values These experiments failed to differentiate the release of histamine from the formation of SRS A this may be because these inhibitors act at a very early stage in the reaction possibly even at the union of antigen with antibody Enzyme antagonists acting on the final reactions actually responsible for the rapid release of histamine of the much slower

formation of SRS A would have much less time to act upon the release mechanism than upon the more continuous process of formation and would thus be expected to be more successful in reducing the yield of SRS A than of histamine

Until a potent (and preferably specific) antagonist is found the importance of SRS A in anaphylaxis cannot be properly assessed but it is clearly of potential importance particularly in human asthma

I have endeavoured to present a critical but rational survey of the humoral factors which may play some part in hypersensitivity reactions It is abundantly clear that great differences exist between these reactions in different tissues and in different species and it is therefore extremely dangerous to argue by analogy in this field Even in the simpler matter of the effects of active substances on various tissues some show a great deal more uniformity of action than others Many of the substances which have been considered are of recent discovery and only limited pharmacological data are available Since these data seldom relate directly to man some recourse to analogy however unsatisfactory cannot be avoided at present if a reasonably complete appraisal of the clinical problems is to be made

In most hypersentivitity reactions particularly those which are prolonged there must be many contributory factors the relative importance of any one of these varying with the stage which the reaction has reached Indeed each stage represents a separate biochemical problem and at present we know only a little about very few

SUMMARY

If a pharmacologically active substance can cause a tissue to respond in a manner which is also known to result from an antigen antibody reaction this fact alone may have little significance However if the active substance can also be shown to exist in the same tissue during the antigen antibody reaction it becomes highly probable that it contributes to the observed effect There is a strong temptation to extend such a conclusion by assuming that similar organs of the same species or the same organ from different species will react in the same way this is frequently invalid and misleading

The probable role of histamine 5 hydroxytryptamine and SRS A (a slow reacting substance) in hypersensitivity states in various tissues and species particularly man is examined critically on the basis of the above criteria The possible participation in certain reactions of other substances such as plasma kinins heparin leucotaxine and permeability factors is considered although definite evidence is scanty Certain of the conclusions reached are as follows —in all cases in which histamine causes an increase in capillary permeability this effect will probably be prolonged by plasma kinins and globulin permeability factors in human asthma the bronchospasm can be accounted for by histamine and SRS A whilst the œdema of connective tissue and increased glandular activity may be caused in part by plasma kinins it is unlikely that 5 HT is important either in asthma

or skin reactions in man prolonged and delayed reactions in skin may involve leucotaxine probably associated with plasma kinins and permeability factors where the adhesion of leucocytes and platelets to the capillary endothelium occurs in the reaction heparin may reduce this

RÉSUMÉ

Lorsqu une substance pharmacodynamique peut provoquer pour un tissu une reaction semblable a celle d un antigene a un anticorps ce fait seul peut n avoir que peu de signification

Cependant si la présence de cette meme substance active dans ce meme tissu au cours de la reaction antigene anticorps est démontrée il devient extremement probable qu elle participe à la production des effets alors observes

On est fortement tente de donner a cette conclusion une portee plus generale en admettant que les memes organes d une meme e pece animale ou les memes organes d autres especes sont appeles a reagir de la meme façon or cela est souvent inexact et peut entrainer des erreurs

Prenant pour bases ces donnees il est procedé a un examen critique du role probable joué pour divers tissus et diverses especes plus particulierement chez l homme dans les etats d hypersensibilité par la 5 hydroxytryptamine et le SRS A (substance a reaction lente)

La possibilite de participation a certaines reactions d autres substances est examinee ainsi que les facteurs determinant la permeabilite bien que les donnees definitivement controlées soient rares (plasma kinine heparine leucotoxine)

L auteur expose certaines des conclusions auxquelles il est parvenu

— dans tous les cas ou l histamine provoque une plus grande permeabilite capillaire la duree de cet effet est vraisemblablement prolongée par les plasma kinines et par le degre de permeabilite des globulines

— dans l asthme chez l homme le spasme bronchique peut etre attribué a l action de l histamine et de la SRS A alors que l œdeme des tissus connexes et l activite glandulaire accrue peuvent etre dus en partie aux plasma kinines

— une action importante de la 5 HT est improbable sur les reactions cutanées ou l asthme chez l homme

— les reactions cutanees de longue duree et différees peuvent impliquer une action de la leucotoxine probablement associée aux plasma kinines et au phénomene de permeabilité

— dans le cas d adhérence de leucocytes et de plaquettes sanguines a l endothélium capillaire l heparine peut exercer une action reductrice

ZUSAMMENFASSUNG

Wenn eine pharmakologisch wirksame Substanz eine Gewebe veranlassen kann in solcher Art und Weise zu reagieren wie man es unter dem Einfluss einer Antigen Antikoperreaktion kennt so hat diese Tatsache an und fur sich geringe Bedeutung Wenn hingegen die aktive Substanz

im gleichen Gewebe wahrend der Antigen Antikorperreaktion nachgewiesen werden kann dann wird es sehr wahrscheinlich dass diese Substanz für den beobachteben Effekt verantwortlich ist Grosse Versuchung besteht eine solche Anschauung durch die Annahme zu erweitern dass gleiche Organe der gleichen Spezies oder ein gleiches Organ von verschiedenen Spezies in gleicher Weise reagieren dies trifft aber oft nicht zu und fuhrt zu falschen Schlussen

Die wahrscheinliche Rolle von Histamin 5 Hydroxytryptamin und SRS-A (eine langsam reagierende Substanz) wird bei Überempfindlichkeitszustanden in den verschiedenen Geweben und bei verschiedenen Spezies besonders beim Menschen kritisch untersucht indem als Grundlage die obigen Kriterien berucksichtigt werden Die mogliche Beteiligung bei gewissen Reaktionen von anderen Substanzen wie Plasma Kinine Heparin Leukotoxin und Permiabilitatsfaktoren wird in Erwagung gezogen obgleich definitive Beweise hierfur nur karglich vorhanden sind Schlusse die man aus den bisherigen Versuchsergebnissen zehen kann — Bei allen Fallen in denen Histamin eine gesteigerte Kapillarpermeabilitat bewirkt wird dieser Effekt durch Plasma Kinine und Globulin Permeabilitatsfaktoren verlangert Beim menschlichen Asthma kann der Bronchospasmus durch Histamin — und SRS A Wirkung erklart werden wahrend das Ödem der Bindegewebe und die gesteigerte Drusentatigkeit zum Teil von Plasma Kininen verursacht werden konnten — Es ist unwahrscheinlich dass 5 HT beim Menschen fur Asthma oder Hautreaktionen von Bedeutung ist — In der Haut konnte Leukotoxin fur verlangerte und verzogerte Reaktionen verantwortlich sein wahrscheinlich gekoppelt mit Plasma Kininen und Permeabilitatsfaktoren —Wo wahrend der Reaktion eine Adhasion an den Endothelien von Leukozyten und Blutplattchen auftritt durfte Heparin dies reduzieren

RESUMEN

El hecho de que una sustancia farmacologicamente activa produzca sobre un tejido un efecto semejante al producido por la reacción antígeno anticuerpo no tiene mucha importancia pero si además dicha sustancia aparece durante la reaccion inmunológica entonces es muy probable que realmente contribuya al efecto observado Generalizar esta conclusión y suponer que órganos similares de una misma especie animal o el mismo organo de diferentes especies reaccionan de la misma manera conduce muy a menudo a resultados falsos

Teniendo en cuenta estas consideraciones el autor examina críticamente el probable papel desempeñado por la histamina la 5 hidroxitriptamina y la SRS A (*slow reacting substance*) en los estados de hipersensibilidad de varios tejidos y especies en particular en el hombre Considera asimismo aunque los datos son escasos la posible participatión de otras sustancias tales las kininas plasmáticas heparina leucotaxina y los factores de permeabilidad *Algunes de las conclusiones son las siguientes* en todos los casos en que la histamina produce un aumento de la permeabilidad capilar este aumento es probablemente prolongado por las kininas plasmaticas y ciertas globulinas el broncospasmo del asma humano puede ser explicado

por la acción de la histamina y de la SRS A en tanto que el edema del tejido conectivo y el aumento de la actividad glandular son debidos parcialmente a las kininas del plasma es poco probable que la 5 HT tenga importancia en el asma o las reacciones cutáneas en el hombre las reacciones de tipo tardío de la piel son producidas por la leucotaxina asociada talvez a las kininas plasmáticas y los factores de prmeabilidad en los casos en que la reacción se acompaña de depósito de leucocitos y plaquetas sobre el endotelio de los capilares la heparina tiende a disminuir este efecto

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HISTAMINE METABOLISM

by

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My presentation will deal with recent work from our laboratory on *(a)* the formation and binding of histamine *(b)* studies on the nature of the regulation of these processes *(c)* a new approach to the evaluation of the role of histamine in allergy and *(d)* some experiments bearing on the mode of action of the antihistamines

At the Second International Congress of Allergology I reported our findings on the effect of the adrenal hormones on histamine formation and binding *in vitro* I will briefly review our work Rats were adrenalectomized or injected intramuscularly with cortisone 5 mg per day for 3 days Two hours after the final cortisone injection (or 3 days following adrenalectomy) the rats were killed tissues minced and the fragments incubated with C^{14} labelled L-histidine The amount of C^{14} histamine produced was determined by isotope dilution assay Normal controls were also run Results are shown below

TABLE I

Histamine Formation in Rat Tissues in vitro
(% increase or decrease relative to normal controls)

	ADRENALECTOMY	CORTISONE	PREDNISONE	PREDNISONE (activity of isolated soluble histidine decarboxylase measured)
Skin	+ 42	— 76		
Lung	+ 104	— 53	— 86	— 79
Stomach	— 53	+ 24		

Like skin and lung abdominal muscle and small intestine formed less histamine under the influence of cortisone however the total amounts

formed were quite small Stomach in contrast to other tissues seems to have histamine production stimulated by cortisone The reason for this is not clear at present However it may be related to the fact that much of the histidine decarboxylase of most tissues may be in mast cells while that of rat stomach is in some other type of cell It has been reported that the glandular portion of rat stomach is almost free of mast cells (1)

In addition to testing the effects of adrenalectomy and cortisone on rat lung the effect of prednisone was studied It produced very strong inhibition of histamine formation which we further found was due to decreased activity of extractible histidine decarboxylase If human lung behaves in a similar manner the therapeutic effect of prednisone in asthma may be explicable at least in part by its strongly inhibitory effect on histidine decarboxylase The mechanism of this inhibition is not yet known Schild and his co workers have produced evidence that histamine is implicated in asthma (2)

Recently we have completed experiments to find if these *in vitro* effects of cortisone and adrenalectomy are valid *in vivo* Rats which had been adrenalectomized hypophysectomized, or treated with cortisone were injected with C^{14} L histidine After two days they were killed and the tissues analyzed for C^{14} histamine Average values for a number of rats are shown in Table II

TABLE II

Effect of Cortisone Treatment Adrenalectomy and Hypophysectomy on Binding of New Histamine by Rat Tissues in vivo
(% increase or decrease relative to normal controls)

	CORTISONE	ADRENALECTOMY	HYPOPHYSECTOMY
Abdominal skin	− 77	+ 50	+ 29
Small intestine	− 54	+ 100	+ 158
Abdominal muscle	− 48	+ 57	+ 30
Stomach	+ 69	− 7	− 18

Thus the results of the *in vitro* studies are largely confirmed in living animals Cortisone treatment reduced the histamine binding of all tissues except stomach in which histamine binding was increased There seems to be no evidence (except possibly for the intestine) that there is any hypophyseal control over histamine binding *in vivo* that is not mediated by the adrenals The finding that cortisone treatment stimulates histamine production in rat stomach may have some bearing on observations elsewhere that *(a)* histamine produces peptic ulcers in animals *(b)* patients treated with cortisone frequently develop peptic ulcers

Some years ago, in evaluating effects of various compounds on *histamine* binding by rat skin *in vitro* we found that pretreatment of the rats with Compound 48/80 a powerful histamine releasing agent caused a marked increase in histamine binding (3) Recently we have started to reinvesti

gate this matter and have been able to demonstrate conclusively that this is due to a marked increase in the activity of the soluble histidine decarboxylase extractable from skin

This result was somewhat unexpected since Compound 48/80 disrupts mast cells and releases their contents (histamine, serotonin granules histidine decarboxylase etc) Investigations are now in progress to see whether this increase in histidine decarboxylase activity is due specifically to Compound 48/80 or wheter it may be caused by any agent affecting the mast cells There are important implications for allergy if it can be shown that the antigen antibody reaction which may disrupt mast cells results in a heightened histidine decarboxylase activity of the tissue with a resultant exposure of the tissue to increased concentrations of histamine Perhaps the time required for the development of the increased histidine decarboxylase activity may correspond to the time elapse in delayed allergic responses

One of our most urgent problems is to devise a method by which meaningful evaluation can be made of the role of histamine formation or release in allergic conditions *in vivo* Assays for histamine itself in blood or urine have led to disappointing results This is to be expected for histamine is rapidly and extensively destroyed after release We now know the identity of the metabolic product of histamine which should be sought

Since the last Congress we have performed quantitative analyses for [illegible]

are as follows

Histamine	2 to 3 %
Methylhistamine	4 to 8
Methylimidazoleacetic acid	42 to 47
Imidazole acetic acid (free plus conjugated)	26 to 33

It is obvious that it would be more fruitful to assay urine for methylimidazoleacetic acid than for histamine itself However there is no known means of analyzing for this compound except by use of isotopic methods

Colorimetric methods for determining imidazoleacetic acid are available however this compound appears to be formed in large quantities from histidine by another metabolic route not involving histamine as an intermediate This has been shown in rats (5) and dogs (6) It is therefore impossible to use imidazoleacetic acid excretion as a criterion of histamine release

We have devised a method for determination of C^{14} methylimidazole acetic acid in urine and tissue extracts of animals which have previously been given C^{14} L histidine The method is specific and the relatively huge concentrations of histidine imidazoleacetic acid, and histidine metabolic products do not interfere It is believed that studies can now be made to follow histamine release during allergic reactions in living animals results will be reported at the Congress

Finally I should like to present some data on antihistamines they were obtained from studies to find if antihistamines influence the various aspects of histamine formation and fate

1 EFFECT OF TRIPELENNAMINE HYDROCHLORIDE ON THE FORMATION AND BINDING OF NEW HISTAMINE IN THE ABDOMINAL SKIN OF INTACT RATS — Rats were fed a diet containing 1 mg tripelennamine HCl per gram After 24 hours on this diet (which was fed throughout the experiment) they were injected with 10 mg tripelennamine HCl per kilogram body weight Then 30 minutes later they were injected with C^{14} L-histidine Seven hours after the histidine they received another 10 mg of tripelennamine HCl Controls received C^{14} histidine but no tripelennamine HCl The rats were killed 24 hours after the histidine injection and the abdominal skin analyzed for C^{14} histamine The values for five tripelennamine HCl treated rats was only 2% lower (not significant) than the controls This is evidence that tripelennamine HCl cannot block the sites where L-histidine is decarboxylated or where the resulting histamine is bound (7)

2 EFFECT OF TRIPELENNAMINE HYDROCHLORIDE ON IN VITRO FORMATION AND BINDING OF C^{14} HISTAMINE BY RAT ABDOMINAL SKIN — Addition of tripelennamine HCl final concentration 200 to 400 γ/ml had no significant effect on the amount of C^{14} histamine formed and bound when minced abdominal skin was incubated with C^{14} L-histidine (2)

3 EFFECT OF PROMETHAZINE HYDROCHLORIDE ON THE ACTIVITY OF HISTIDINE DECARBOXYLASE — Histidine decarboxylase was obtained in soluble form from the free mast cells of rat peritoneal fluid (8) Promethazine HCl added to the incubates to give a final concentration of 100 γ/ml had no detectable inhibitory effect (7)

4 EFFECT OF PROMETHAZINE HYDROCHLORIDE ON HISTAMINE RELEASE — In this study we showed that (*a*) promethazine HCl does not releases histamine (*b*) promethazine HCl does not prevent the release of histamine induced by compound 48/80 (9)

5 EFFECT OF TRIPELENNAMINE HYDROCHLORIDE ON HISTAMINE CATABOLISM IN MICE — When mice were given 0 5 mg tripelennamine HCl intraperitoneally they showed no abnormality in the pattern of urinary metabolites of C^{14} histamine (as detected by paper chromatography) (10)

6 EFFECT OF TRIPELENNAMINE HYDROCHLORIDE ON THE RATE OF DESTRUCTION OF C^{14} HISTAMINE IN MICE — Mice were injected with 0 5 mg tripelennamine HCl intraperitoneally and after 20 minutes injected intraperitoneally with 1 00 γ C^{14} histamine They were killed exactly 15 minute after the histamine injection and immediately frozen in dry ice acetones C^{14} histamine remaining in the entire carcass was determined Four tripelennamine HCl treated mice 64 % of the histamine was metabolized in 15 minutes for controls 66 % (7)

Since we have failed to find any effect of antihistamines on formation binding release catabolism or rate of destruction we conclude as have most others that antihistamines act by occupying and blocking receptors at which histamine exerts its pharmacological activities

SUMMARY

When rats are injected with C^{14} L histidine a small per cent is converted to C^{14} histamine which is bound in the tissues When this binding of new C^{14} histamine in normal rats is compared to that in adrenalectomized rats or cortisone treated rats it was found that adrenalectomy increased histamine binding in abdominal skin adbominal muscle and small intestine but not in stomach Conversely cortisone treatment caused a decrease in histamine binding in all tissues tested except stomach where a marked increase was found These *in vivo* studies confirm most of the earlier *in vitro* studies we have reported

Compound 48/80 a poverful histamine release agent if injected repeatedly into rats is capable of reducing the histamine content of skin to a very low value We have now found that skin from rats thus treated has many times as much extractable histidine decarboxylase activity as normal skin There are possibly important implications of this finding for research in allergy these will be discussed

One of our most urgent problems is to devise a method by which meaningful evaluation can be made of the role of histamine formation or release in allergic conditions *in vivo* Since histamine itself when formed or released is rapidly destroyed it is necessary to seek a metabolic product The major metabolite of histamine in most species tested is methylimidazoleacetic acid We have now devised a method for determining this compound Studies on histamine formation and release *in vivo* will be reported

Investigations on various antihistamines have failed to show any effect on formation bindings release catabolism or rate of destruction of histamine

RÉSUMÉ

Lors de l injection a des rats de L histidine C 14 un faible pourcentage du produit injecte se transforme en histamine C 14 qui se fixe dans les tissus En comparant chez des rats normaux le taux de fixation de cette forme d histamine C 14 avec celle notée chez des rats sur lesquels la surrenalectomie a éte pratiquée ou ayant subi un traitement de cortisone on remarque que la surrenalectomie augmente la fixation de l histamine dans la peau de l abdomen les muscles abdominaux et l intestin grêle mais pas dans l estomac

Le traitement par la cortisone au contraire provoque une diminution de la fixation de l histamine dans les tissus examinés sauf dans l estomac ou l on note une considerable augmentation Ces expériences realisees *in vivo* confirment presque tous les résultats obtenus *in vitro*

Les injections répétees du composé 48/80 qui est un puissant agent hista

Ces observations pourraient avoir dans le domaine de la recherche allergologique des consequences importantes que nous nous proposons de discuter

La mise au point d une methode permettant d évaluer de façon significative le role de la libération et de la formation d histamine chez les aller [illegible]

liques Chez la plupart des especes animales sur lesquelles nos experiences ont ete realisées le principal metabolite est l acide methyl imidazol acetique Nous avons maintenant mis au point un procede pour la determination de ce compose Nous rendrons compte de nos travaux sur la formation et la libération de l histamine *in vivo*

Des experiences faites avec divers produits antihistaminiques ont montre que ces corps sont depourvus d action exercée sur la formation la fixation la liberation le catabolisme ou le taux de destruction de l histamine

ZUSAMMENFASSUNG

Wenn man Ratten Histidine C 14 L injiziert so wird ein geringer Prozentsatz des Injizierten Substanz in Histamin C 14 umgewandelt das sich in den Geweben bindet Vergleicht man dir Bindung dieses neuen Histamins C 14 bei normalen Ratten mit der Fixierung bei Ratten denen man die Nebennieren entfernte oder dit mit Cortison behandelt wurden, so kann man feststellen dass die Nebennierenentfernung die Bindung der Substanz in der Abdominalhaut der Abdominalmuskulatur und im Dunndarm fordert jedoch nicht im Magen

Dagegen ergeuzt eine Cortisonbehandlung eine Verminderung der Fixierung in den intersuchten Geweben ausgenommen am Magen wo man eine erhohte Bindung feststellen kann Diese an lebenden Tieren angestellten Versuche bestatigten fest alle im Laboratorium erhaltenen *in vitro* Resultate

Wiederholte Injektionen der Substanz 48/80 die stark histaminfrei et zend wirkt fuhren zu einem sehr niederigen Histaminspiegel in der Haut von Ratten Es ist moglich aus der Haut der so behandelten Ratten Histidin De carboxylase in im Vergleich zu normalen Ratten mehrfach grosserer Quantitat zu extrahieren

Es kann sein dass die Resultate dieser Versuche fur das Gebiet der Allergieforschung wichtige Folgerungen mit sich bringen die wir diskutieren wollen

Die Ausarbeitung einer Methode die uns gestattet bei lebenden allergischen Tieren die Rolle der Freisetzung und Bildung von Histamin zu studieren und zu verfolgen scheint uns zur Losung der Probleme sehr dringlich

Da man im Organismus eine rasche Zerstorung des freigesetzten oder gebildeten Histamins sieht ist es notwendig diesen Effekt mit einem Stoffwechselprodukt in Zusammenhang zu bringen Bei den meisten Tierarten mit denen wit unsere Versuche anstellten ist die hauptsachliche Stoffwechselsubstanz die Methylimidazolessigsaure Wir haben nun ein Verfahren

zur Bestimmung dieser Verbindung ausgearbeitet Über unsere Arbeiten der Bildung und Freisetzung des Histamins im lebenden Organismus werdeen wir berichten

Versuche mit verschiedenen Antihistamin Substanzen liessen keinerlei Einfluss auf Bildung Bindung Freisetzung Katabolismus oder Zersto rungsintensitat von Histamin erkennen

RESUMEN

Un pequeño porcentaje de la l histidina marcada con carbono 14 inyectada en las ratas es transfromada en C^{14} histamina y fijada por los tejidos En las ratas adrenalectomizadas se encuentra una mayor cantidad de histamina fijada en la piel abdominal los musculos abdominales y el intestino delgado pero no en el estómago y por el contrario en las ratas tratadas con cortisona hay una disminución de la histamina que se fija en los tejidos a excepción del estómago donde la cantidad aumenta Estos estudios «in vivo» confirman la mayor parte de los resultados previos obte nidos «in vitro»

La sustancia llamada 48/80 que es un potente liberador de histamina inyectada repetidamente a las ratas puede reducir considerablemente el contenido en histamina de la piel y se encuentra en estos casos un aumento considerable de la cantidad de decarboxilasa con respecto a la piel normal El autor discute las posibles implicaciones de este hecho

Uno de los problemas más urgentes es el de desarrollar un metodo que permita valorar la formación o liberación de histamina «in vivo» Dado que la histamina es rapidamente destruida es necesario investigar sus metabo litos de los cuales el acido metil imidazol acético es el mas importante en varias especies estudiadas El autor se refiere a un método de dosaje de este compuesto y a los resultados obtenidos de su aplicación

No ha podido encontrarse ninguna acción debida a los antihistamínicos sobre la formación fijacion producción catabolismo o velocidad de destruc ción de la histamina

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SUBSTANCES HISTAMINO LIBÉRATRICES ET PROCESSUS DE LIBÉRATION D HISTAMINE ENDOGÈNE

par

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Depuis que Best Dale et leurs collaborateurs (1) ont démontre la présence de l histamine dans les divers tissus des mammiferes il etait devenu evident que cette substance a l instar des autres amines biogenes devait intervenir dans la regulation de fonctions physiologiques et dans l initiation de processus pathologiques Le role de l histamine dans le controle de certains phenomenes physiologiques bien que maintes fois affirme n a jamais éte demontre comme un fait certain

Par contre on dispose actuellement d un faisceau convergent de preuves qui ne laissent subsister aucun doute sur la participation preéminente de l histamine au declenchement de divers états pathologiques qui s integrent soit dans le large groupe de l inflammation soit dans celui plus limité et plus specifique des reactions allergiques

A cet égard il faut souligner ici l importance toute particuliere des travaux de Thomas Lewis (2) dont les recherches aussi ingenieuses qu approfondies ont apporte des 1927 les preuves indiscutables de la réalité de la libération de l histamine endogene sous l effet de diverses agressions Depuis cette periode les travaux sur le role les conditions et le mécanisme de la liberation de l histamine se sont multipliés a une cadence rarement observee dans l histoire des sciences Ces travaux par leur nombre et leur qualité apportent une preuve eclatante de la fecondité et de la richesse exceptionnelle des idees conçues par Sir Henry Dale (3) car elles embrassent l ensemble du grand probleme de l hypersensibilite

Il n est certes pas possible dans le cadre limité de cet expo e d étudier la question de la libération de l histamine sous tous les aspects Le sujet est bien trop vaste Nous limiterons donc ce rapport a l etude de la libera tion de l histamine par les corps chimiques relativement simples pour les quels un nouveau groupe pharmacodynamique vient d etre cree celui des *substances histamino liberatrices* En fait nos connaissances sur les pro priétés des substances histamino-libératrices ne se sont developpées qu au

cours de ces dernières années. Les résultats déjà acquis soulignent l'intérêt de ces corps pour approfondir et étendre nos conceptions sur le déterminisme biochimique des réactions d'hypersensibilité.

Après avoir résumé les notions actuelles sur les formes biochimiques de l'histamine, nous esquisserons une classification chimique et physiologique des substances histamino-libératrices. Nous étudierons ensuite les modalités et les conditions de la libération de l'histamine et occasionnellement des autres médiateurs par ces substances; nous discuterons enfin les relations entre les processus de déplétion de l'histamine et les phénomènes anaphylactiques et allergiques.

A. FORMES BIOCHIMIQUES DE L'HISTAMINE

La quantité totale d'histamine présente dans l'organisme animal peut être évaluée à environ 2 à 3 mg p. 100 g, bien qu'on constate des variations importantes à cet égard d'une espèce à l'autre. Dans le tableau I sont rapportés les taux d'histamine dans les divers tissus de Rat albinos trouvés dans notre laboratoire (4).

TABLEAU I

Taux d'histamine (exprimés en bichlorhydrate) dans les divers tissus de Rat albinos

TISSU	µg/g	QUANTITÉ TOTALE DANS LE TISSU µg p. 100 g de poids corporel
Plasma	0,1	0,4
Éléments figurés du sang (hématies, leucocytes, plaquettes)	0,4	1,6
Myocarde	8,7	4,3
Foie	3,9	17,9
Estomac	43	25,8
Iléon	13	75,4
Côlon	10,1	20,2
Rein	4,75	3,8
Peau (abdominale)	85	1 275
Poumons	9,7	9,2
Muscle strié	11,6	522
Cerveau	0,2	—
Urines pour 24 heures		15

On peut inférer des chiffres rapportés dans le tableau ci-dessus que: 1° la grande masse d'histamine se trouve dans la peau, la musculature striée et le tube digestif; 2° les organes les plus riches en histamine sont par ordre décroissant: le tégument cutané, le tube digestif, le muscle strié, le poumon, le rein et le foie; 3° le système nerveux central ne contient que des quantités infimes d'histamine.

Les cellules basophiles en général et les mastocytes en particulier, ont une teneur particulièrement élevée en histamine (5), mais il est certain

que d autres éléments cellulaires en contiennent des quantités plus ou moins importantes suivant le tissu et aussi suivant l espèce animale

On ne sait pas encore exactement sous quelle forme biochimique l histamine se trouve à l intérieur des cellules L hypothèse d une liaison purement ionique est très séduisante mais elle n explique sûrement pas comment l histamine est libérée de ses attaches lors de la réaction antigène anticorps ou par certaines substances histamino libératrices On est forcé d admettre (6) que l histamine se trouve à l intérieur des cellules en grande partie sous la forme d un précurseur labile mais qu une autre partie reste chimiquement liée aux structures protoplasmiques dont elle ne peut être séparée que par destruction de la cellule et un traitement avec des réactifs chimiques brutaux

Il convient avant d aller plus loin d envisager ici une autre notion fondamentale de nature physiologique et que nous devons à Dale la différence entre l histamine *intrinsèque* et *extrinsèque* D après Dale (7) l histamine *intrinsèque* est libérée par la cellule même qui est apte à réagir à celle ci Ainsi l histamine libérée par la fibre musculaire lisse peut agir directement sur cette fibre Par contre lorsque l histamine est libérée par un organe à distance et qu elle est apportée aux éléments réactionnels par le courant sanguin il s agit d histamine *extrinsèque* Il est fort plausible que les modalités d action physiologique de l histamine *intrinsèque* et *extrinsèque* en raison de leurs concentrations locales très différentes et aussi en raison de la manière dont elles abordent les récepteurs spécifiques soient *qualitativement* différentes Cette conception éclaire d une nouvelle lumière certains faits physiopathologiques et fournit une explication satisfaisante de l inefficacité relative des antagonistes de l histamine dans certains syndromes allergiques expérimentaux et cliniques

B SUBSTANCES HISTAMINO LIBÉRATRICES

Dans une récente monographie Paton (8) a tenté de donner une classification chimique des substances histamino libératrices

Dans le tableau II nous avons réuni en nous inspirant de la classification de Paton la liste des principales substances histamino libératrices

a) *Relation entre la structure chimique et l activité histamino libératrice*

La propriété histamino libératrice n est pas l apanage d un groupe chimique particulier Un grand nombre de substances histamino libératrices sont des amines des amidines des guanidines des ammoniums quaternaires Dans ce groupe le support de la propriété essentielle est constitué par le radical basique non ionisé et la grandeur de l activité dépend de la longueur de la chaîne carbonée aliphatique le maximum d activité étant en général l attribut des composés en C^8 à C^{18} Les relations entre structure et activité ont une curieuse analogie avec celles qu on observe dans la série des substances curarisantes Les substances les plus intéressantes sont des amines aromatiques substituées parmi celles ci le 48/80 (9) et le 1935 L (10) constituent les composés les plus actifs que nous ayons

D une manière très générale la propriété histamino libératrice apparaît lorsque, dans une molécule les radicaux basiques sont multipliés à des distances suffisantes ou lorsque des radicaux basiques sont attachés à des noyaux aromatiques substitués (8)

TABLEAU II

Classification de substances histamino-libératrices (modifiée d'après Paton)

SUBSTANCES A FAIBLE POIDS MOLÉCULAIRE	SUBSTANCES MACROMOLÉCULAIRES
Monoamines $NH_2-(CH_2)_n-CH_3$ $n = 2$ à 12	Complexe antigène anticorps
	Ovomucoïde (Rat)
Diamines $NH_2-(CH_2)_n-NH_2$ $n = 2$ à 16	Dextran (Rat)
Diamidines NH_2 CH_2 $(CH_2)_n$ NH CH $n = 8$ à 16	Polyvinylpyrrolidone (Chien) Tween 20 (Chien) Peptones (Chien)
Composés biquaternaires $(CH_3)_3N-(CH_2)_n-N(CH_3)_3$ $n = 12$	Anaphylatoxine (Cobaye)
Amines aromatiques substituées 48/80 $OCH_3-C_6H_3(CH_3)-CH_2-CH_2-N(CH_3)H$	Polymyxine Ferments protéolytiques Venins et toxines
1935 L $OH-C_6H_4-CH(C_6H_3(CH_3)OH)-CH_2-CH(CH_3)-NH_2$	
Ammonium *d* Tubocurarine Licheniformine Sinoménine Morphine Trimetophan	

Un groupe à part, mais non le moins intéressant, est constitué par les substances macromoléculaires (6). Il n'y a pas lieu de s'arrêter sur les composés biologiques complexes tels que les ferments, les venins, les toxines, etc. : ici la libération de l'histamine est un phénomène contingent et elle est secondaire à la destruction ou à la dislocation des protéines cellulaires. Par contre, certains polymères naturels ou synthétiques méritent un intérêt particulier en raison de la similitude de leurs effets avec la réaction antigène-anticorps et aussi à cause de leur grande spécificité d'action.

C est parce que par certains aspects physiologiques et peut etre aussi par le mecanisme d action les substances macromoléculaires diffèrent des amines basiques et des alcaloides que nous avons préféré à une classification chimique encore impossible une division en *substances à poids moléculaire faible* et en *substances macromoléculaires*

b) *Caracteres physiologiques genéraux*

Il y a lieu de souligner d emblée que la sensibilité de diverses especes animales à l égard de substances histamino libératrices varie considera blement Ainsi le Rat le Chien et le Chat réagissent promptement à ces substances alors que le Cobaye le Lapin la Souris sont plus ou moins réfractaires L Homme réagit par un syndrome typique à toute une série de ces substances 1935 L 48/80 stimbamidine d tubocurarine etc

Cette spécificite de l espèce est meme plus frappante avec les substances macromoléculaires ainsi l ovomucoide et le dextran agissent seulement chez le Rat alors que le Tween 20 et la polyvinylpyrrolidone ne provoquent leurs effets essentiels que chez le Chien l anaphylatoxine est douee de pro priétés histamino libératrices chez le Cobaye seulement La raison et la nature de cette spécificite de l espèce restent entièrement inexpliquees

c) *Symptomatologie*

Les symptomes provoqués par les substances histamino liberatrices varient d une espece animale à l autre mais ils sont identiques chez la meme espèce quel que soit le produit utilisé

L intensité des troubles depend de la voie d introduction et de la dose Chez le Rat l injection intraveineuse d une dose suffisante de 48/80 de 1935 L de dextran ou de toute autre substance histamino liberatrice produit les symptomes généraux d un collapsus vasculaire avec cyanose hémoconcentration et hypothermie Lorsque les substances sont adminis trées par voie peritonéale elles produisent un tableau clinique très caracté ristique prurit généralisé érytheme suivi d œdème des extrémités et plus particulierement des pattes du museau des oreilles de la langue des organes génitaux Le denominateur commun de tous ces troubles est une augmentation brusque de la perméabilité capillaire Celle ci peut etre visualisée par l administration de certains colorants macromoleculaires tels que le bleu d Evans qui s accumulent électivement dans les zones ou se produit l œdeme en causant un « bleuissement » de ces zones (12 13) Dans les memes conditions l injection intradermique locale de ces substances determine une alteration locale de la perméabilité capillaire qui se traduit par de l œdeme et le depot local du colorant

Chez le Chien (9 10) l injection intraveineuse d une substance hista mino libératrice produit un tableau véritablement dramatique quelques minutes après l injection le prurit est intense la peau devient érythémateuse et se couvre de plaques d urticaire Un œdème apparait autour du museau des yeux et des oreilles Souvent un état de prostration et de collapsus suit ces phenomènes

Chez le Chat les symptomes cliniques sont assez similaires prurit

salivation prostration et plus tard au moment du rétablissement, œdeme du nez et des paupières

Chez tous les animaux, on observe une augmentation de la secretion gastrique

Si l on enregistre la pression arterielle on observe a la suite de l injection intraveineuse d une substance histamino libératrice une baisse rapide et intense de la pression arterielle Il y a lieu de retenir un détail important et tres significatif l hypotension ne se produit que 30 a 150 secondes apres l injection (14) Cette période de latence qu on observe avec toutes les substances histamino liberatrices signifie que la substance n a pas d action directe sur le reseau vasculaire mais que l hypotension releve d un mecanisme indirect lié a la libération de l histamine endogene

La notion de la dose seuil est d une grande importance pour ce groupe de substances et elle est surtout évidente lorsqu on a recours a la voie intraveineuse Si l on introduit les substances par voie veineuse il convient de les administrer avec une vitesse suffisante sans quoi les phénomènes cliniques ne se produisent pas

La repétition des injections conduit a un état refractaire Bien souvent l injection seconde de la meme dose demeure inopérante si elle est pratiquée dans les heures qui suivent la première Par des injections convenablement réiterées on parvient à accroitre la tolerance et a créer un état réfractaire qui peut persister plusieurs jours

C MODALITÉS DE LA LIBÉRATION DE L HISTAMINE ENDOGÈNE

On possede actuellement toute une série d épreuves qui permettent de vérifier les proprietes histamino liberatrices d une substance Certaines sont basées sur des tests *in vitro* alors que d autres les plus importantes sont établies chez l animal *in vivo*

Lors de la mise en contact *in vitro* des substances histamino libératrices avec divers tissus intacts (15 16 (17) ou divisés en tranches (18) il se produit une diffusion de l histamine intracellulaire dans le milieu ambiant La perfusion des tissus permet d obtenir également une decharge de l histamine endogene C est une technique souvent plus efficace et dans certaines conditions relativement quantitative (19 20 (21)

Quel que soit l interet de ces techniques *in vitro* elles ne doivent etre considérees que comme etant complémentaires des epreuves *in vivo* En effet l injection de substances histamino libératrices produit une décharge de l histamine intracellulaire qui se traduit par une inflation en histamine du compartiment extracellulaire L augmentation du taux de l histamine plasmatique reflete dans une certaine mesure l importance de la libération de l histamine tissulaire

La *figure 1* illustre les modifications de l histamine plasmatique observées chez le Rat le Chien et l Homme apres injection de 1935 L La liberation de l histamine est un phénomène rapide quasi explosif et le maximum est atteint dans les cinq minutes qui suivent l injection Ultérieurement le taux de l histamine plasmatique décroit progressivement et lentement et ce n est qu apres deux a quatre heures qu il approche des valeurs normales

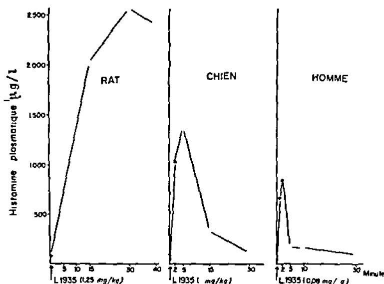


FIG 1 — Modifications du taux de l histamine plasmatique apres injection intra veineuse de 1935 L chez le Rat (1 25 mg/kg) chez le Chien (1 mg/kg) et chez l Homme (0 08 mg/kg)

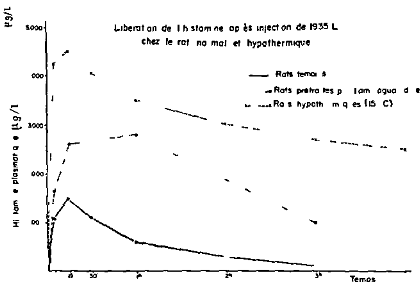


FIG 2 — Taux de l histamine plasmatique après injection de la même dose de 1935 L (250 µg/100 g par voie intraveineuse) chez un groupe de rats témoins chez un groupe de rats normothermes prétraités par l α aminoguanidine et chez un groupe de rats maintenus en état d hypothermie (15 °C)

Sous l influence de l α aminoguan dine l hyperhistaminémie plasmatique est beau coup plus importante et aussi plus durable L hyperhistaminémie est encore plus accusée et ne baisse que tres lentement chez les animaux en état d hypothermie

salivation, prostration et, plus tard, au moment du rétablissement, œdème du nez et des paupières.

Chez tous les animaux, on observe une augmentation de la sécrétion gastrique.

Si l'on enregistre la pression artérielle, on observe, à la suite de l'injection intraveineuse d'une substance *histamino-libératrice*, une baisse rapide et intense de la pression artérielle. Il y a lieu de retenir un détail important et très significatif : l'hypotension ne se produit que 30 à 150 secondes après l'injection (14). Cette période de latence qu'on observe avec toutes les substances *histamino-libératrices* signifie que *la substance n'a pas d'action* directe sur le réseau vasculaire mais que l'hypotension relève d'un mécanisme indirect lié à la libération de l'histamine endogène.

La notion de la dose seuil est d'une grande importance pour ce groupe *de substances et elle est surtout évidente lorsqu'on a recours à la voie intraveineuse.* Si l'on introduit les substances par voie veineuse, il convient de les administrer avec une vitesse suffisante, sans quoi les phénomènes cliniques ne se produisent pas.

La répétition des injections conduit à un *état réfractaire.* Bien souvent l'injection seconde de la même dose demeure inopérante si elle est pratiquée dans les heures qui suivent la première. Par des injections convenablement réitérées, on parvient à accroître la tolérance et à créer un état réfractaire qui peut persister plusieurs jours.

C. MODALITÉS DE LA LIBÉRATION DE L'HISTAMINE ENDOGÈNE

On possède actuellement toute une série d'épreuves qui permettent de vérifier les propriétés histamino-libératrices d'une substance. Certaines sont basées sur des tests *in vitro*, alors que d'autres, les plus importantes, sont établies chez l'animal *in vivo*.

Lors de la mise en contact *in vitro* des substances histamino-libératrices avec divers tissus intacts (15, 16, 17) ou divisés en tranches (18), il se produit une diffusion de l'histamine intracellulaire dans le milieu ambiant. La perfusion des tissus *permet d'obtenir également* une décharge de l'histamine endogène. C'est une technique souvent plus efficace et, dans certaines conditions, relativement quantitative (19, 20, 21).

Quel que soit l'intérêt de ces techniques *in vitro*, elles ne doivent être considérées que comme étant complémentaires des épreuves *in vivo*. En effet, l'injection de substances histamino-libératrices produit une décharge de l'histamine intracellulaire qui se traduit par une inflation en histamine du compartiment extracellulaire. L'augmentation du taux de l'histamine plasmatique reflète, dans une certaine mesure, l'importance de la libération de l'histamine tissulaire.

La figure 1 illustre les modifications de l'histamine plasmatique observées chez le Rat, le Chien et l'Homme après injection de 1935 L. La libération de l'histamine est un phénomène rapide, quasi explosif et le maximum est *atteint dans les cinq minutes qui suivent l'injection.* Ultérieurement, le taux de l'histamine plasmatique décroît progressivement et lentement et ce n'est qu'après deux à quatre heures qu'il approche des valeurs normales.

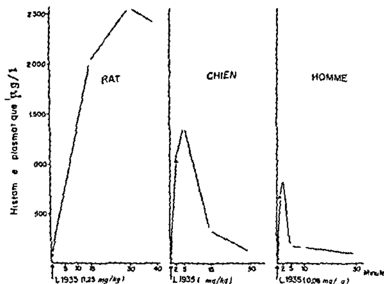


FIG 1 — Modifications du taux de l histamine plasmatique apres injection intra veineuse de 1935 L chez le Rat (1 25 mg/kg) chez le Chien (1 mg kg) et chez l Homme (0 08 mg/kg)

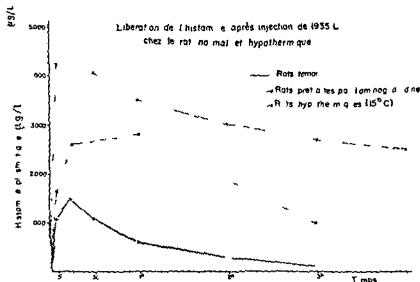


FIG 2 — Taux de l histamine plasmatique après injection de la même dose de 1935 L (250 µg/100 g par voie intraveineuse) che. un groupe de rats témoins chez un groupe de rats normothermes prétraités par l α aminoguanidine et chez un groupe de rats maintenus en état d hypothermie (15 °C)
Sous l influence de l α am noguanidine l hyperhistaminémie plasmatique est beau coup plus importante et aussi plus durable L hyperhistaminémie est encore plus accusée et ne baisse que tres lentement chez les animaux en état d hypothermie

La cinétique et l importance de la libération de l histamine endogène est en corrélation étroite avec la symptomatologie clinique.

L histamine libérée subit rapidement une destruction enzymatique. Celle-ci peut être en grande partie empêchée soit par un prétraitement avec l α aminoguanidine soit par l hypothermie.

La figure 2 illustre les modifications des taux de l histamine plasmatique,

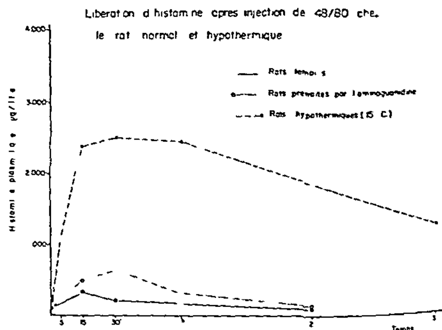


Fig 3 — Modifications des taux de l histamine plasmatique après injection intraveineuse de la même dose de 48 80 (15 µg/100 g) chez un groupe de rats témoins, chez un groupe d animaux normothermes prétraités avec l α-aminoguanidine et un groupe d animaux maintenus en hypothermie (15 °C).
La dose de 48 80 a été choisie très faible afin d obtenir un effet liminaire Ceci met en valeur l action remarquable de l'hypothermie qui est bien plus considérable que celle de l α aminoguanidine

après injection de la même dose de 1935 L chez l animal de contrôle après prétraitement par l α aminoguanidine et chez l animal dont la température a été abaissée à 15° C Le prétraitement par l α aminoguanidine a pour résultat non seulement une augmentation de l hyperhistaminémie mais aussi sa prolongation Mais plus remarquable encore à cet égard est l effet de l hypothermie Chez l animal en hypothermie l hyperhistaminémie est 3 fois plus élevée et elle se maintient à ce taux pendant des heures, les processus de destruction et d élimination étant pratiquement bloqués.

L influence de l hypothermie sur la libération de l histamine par le 48/80 est encore plus évidente

Ainsi qu il ressort des chiffres rapportés dans la figure 3 la dose liminaire histamino-libératrice de 48/80 chez l animal normotherme est de 15 à 20 µg/100 g À cette dose la mortalité est nulle Chez l animal en hypo-

thermie cette dose de 48/80 provoque une augmentation importante de l histamine plasmatique et fait curieux la toxicité de ce corps devient considerable puisque à la dose de 15 γ p 100 g 42 p 100 des animaux hypo

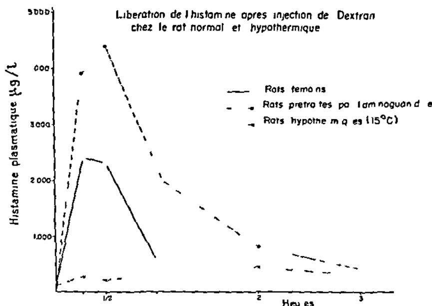


FIG 4 — Modifications des taux de l histamine plasmatique après injection intraveineuse de la même dose de dextran (180 mg p 100 g) chez un groupe de rats témoins chez un groupe de rats normothermes mais prétraités avec l α amino guanidine et chez un groupe d animaux maintenus en état d hypothermie (15 C) Le pretraitement avec l α aminoguanidine augmente et prolonge l hyperhistaminémie Contrairement à ce qui se passe avec le 48/80 et le 1935 L l hypothermie supprime la libération de l histamine provoquée par le dextran

thermiques succombent trois heures apres l injection L explication de ce phénomene reste encore à fournir

Si l hypothermie exagere d une maniere considerable les taux de l histamine endogène circulante — vraisemblablement par inhibition de sa destruction et de son élimination — *lors de l emploi de* 1935 *L ou de* 48/80 *il n en est pas de meme pour le dextran Chez l animal en hypothermie l injection de dextran n est pas suivie de l augmentation de l histamine plasmatique regulierement observée chez l animal normotherme ainsi que le montre la figure* 4

Cette divergence est constante et elle met en évidence d une maniere frappante le mode d action *different* des substances histamino liberatrices suivant leur taille moléculaire

Quelle est la signification physiologique de ce phénomene? Il est impossible de repondre avec certitude à l heure actuelle a cette question Il convient seulement de rappeler ici que le choc anaphylactique est régulièrement inhibé en hypothermie

Les modifications de l histamine plasmatique ne peuvent constituer qu un indice de la mobilisation et des mouvements de l histamine Elles ne

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L histamine liberee subit rapidement une destruction enzymatique. Celle ci peut etre en grande partie empechee soit par un pretraitement avec l α aminoguanidine soit par l hypothermie

La figure 2 illustre les modifications des taux de l histamine plasmatique

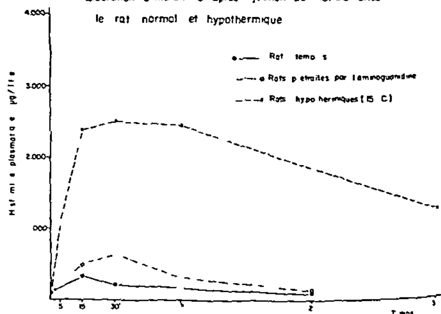


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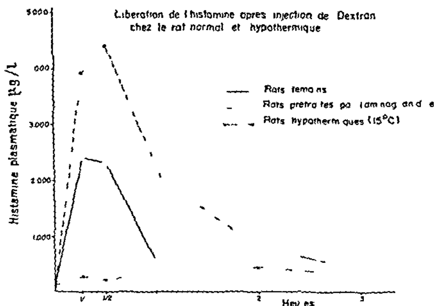


FIG 4 — Modifications des taux de l'histamine plasmatique après injection intraveineuse de la même dose de dextran (180 mg p. 100 g) chez un groupe de rats témoins chez un groupe de rats normothermes mais prétraités avec l'α aminoguanidine et chez un groupe d'animaux maintenus en état d'hypothermie (15 °C). Le prétraitement avec l'α aminoguanidine augmente et prolonge l'hyperhistaminémie. Contrairement à ce qui se passe avec le 48/80 et le 1935 L. l'hypothermie supprime la libération de l'histamine provoquée par le dextran

thermiques succombent trois heures après l'injection. L'explication de ce phénomène reste encore à fournir

Si l'hypothermie exagère d'une manière considérable les taux de l'histamine endogène circulante — vraisemblablement par inhibition de sa destruction et ... *il n'en est pas* ... *tion de dextran* ... *régulièrement observée chez l'animal normotherme ainsi que le montre la figure 4*

Cette divergence est constante et elle met en évidence d'une manière frappante le mode d'action *différent* des substances histamino-libératrices suivant leur taille moléculaire

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Les modifications de l'histamine plasmatique ne peuvent constituer qu'un indice de la mobilisation et des mouvements de l'histamine. Elles ne

nous renseignent guere sur la quantite d histamine mise en liberte Seule la mesure de l histamine éliminée dans les urines est susceptible de nous donner ce renseignement a condition d empecher sa destruction enzymatique dans l organisme par l administration d un inhibiteur de la diamino oxydase

L etude de l élimination urinaire de l histamine a revéle que la quantite d histamine urinaire, par 24 heures, est chez le Rat de l ordre de 15 µg p 100 g de poids corporel Soixante p 100 environ de cette quantité d histamine se trouvent sous forme libre et 40 p 100 sous forme conjuguée Sous l effet de l injection d une substance histamino libératrice telle que le 1935 L la quantite d histamine éliminée passe a environ 200 µg par 24 heures pour 100 g de poids corporel La presque totalité de l histamine éliminée se trouve sous forme libre (fig 5)

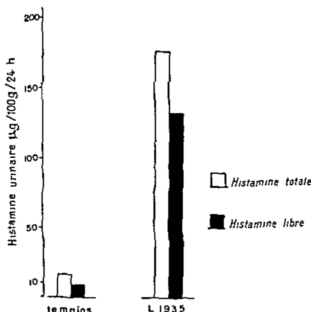


FIG 5 — Rats prétraités avec l α aminoguanidine
A gauche elimination urinaire d histamine par 100 g p 24 h chez les animaux témoins
A droite élimination urinaire apres injection intrapéritonéale de 1 mg p 100 g de 1935 L

La derniere preuve et non la moindre, de la mobilisation de l histamine cellulaire est l appauvrissement des tissus en histamine après injection de substances histamino libératrices Les premières recherches de Feldberg et Talesnik (22) ont montré que les injections répétées de 48/80 produisent une diminution sensible de la teneur en histamine de divers tissus chez le Rat Cependant un traitement meme prolongé et intensif ne parvient pas à ramener ce taux d histamine à zéro (23) Ce fait a été confirmé par divers auteurs soit avec le 48/80 soit avec d autres substances histamino libératrices (6) *dont la plupart sont d ailleurs, à cet égard, moins actifs que le

48/80. Cependant, dans des expériences utilisant la perfusion de la peau on peut parvenir à débarrasser quasi complètement les tissus de leur histamine cellulaire (24). Il convient de mentionner ici que les divers tissus ne lâchent pas l'histamine avec la même facilité ; ainsi, chez le Chat, la déplétion de l'histamine peut être réalisée complètement dans la peau ; elle est moins complète dans le muscle strié, les poumons, le myocarde ; le foie, par contre, il est presque impossible d'obtenir la baisse du taux de l'histamine du tube digestif (24). La raison de cette différence reste encore obscure.

La resynthèse de l'histamine tissulaire après sa déplétion est un processus lent, tout au moins chez le Rat.

Les travaux de Schayer (25, 26, 27, 28) *ont montré que c'est à partir* de l'histidine qu'est réalisée la formation de l'histamine cellulaire. Ce processus de biogenèse est fortement influencé par les hormones corticosurrénaliennes : la cortisone le retarde alors que la DOCA le favorise (29) (30, 31).

D. ÉTAT RÉFRACTAIRE ET PROTECTION CROISÉE

La répétition des injections de substances histamino-libératrices conduit à l'apparition d'un état réfractaire (22). Tous les troubles physiologiques produits par la substance histamino-libératrice : hypotension, hémoconcentration, hypersécrétion gastrique, prostration, hypothermie s'atténuent au fur et à mesure qu'on réitère, à des intervalles adéquats, les injections de ces substances. Il est infiniment probable que l'installation de cet état réfractaire est conditionné par la déplétion de l'histamine tissulaire. Mais cette explication n'est pas acceptable dans tous les cas. Ainsi, chez le Chien, une seule injection d'une dose suffisante d'une substance histamino-libératrice détermine un état réfractaire à l'égard de cette substance, état qui peut persister durant 24 heures et davantage. La figure 6 montre un tel effet du 1935 L sur la pression artérielle chez le Chien.

Il est exclu que ce phénomène de tachyphylaxie rapide soit dû à un épuisement de l'histamine endogène. Feldberg et Talesnik (22), nous-même (6) et d'autres ont bien vu que, pour obtenir une déplétion tissulaire d'histamine d'une certaine importance, il faut multiplier les injections pendant une longue période. Plusieurs hypothèses peuvent être invoquées pour expliquer cet état réfractaire rapide : absence d'une libération d'histamine, inactivation de l'histamine libérée par un autre constituant libéré simultanément, ou encore modification de la réactivité cellulaire à l'égard de la substance, comme on le voit dans d'autres exemples de tachyphylaxie.

Paton (8), qui admet lui aussi l'impossibilité d'*attribuer l'état réfractaire* immédiat à une déplétion de l'histamine, suggère deux explications possibles : l'héparine cellulaire libérée bloquerait l'histamine ou encore les cellules seraient devenues insensibles à l'histamine.

Les résultats de dosages d'histamine plasmatique rapportés dans la figure 6 montrent clairement qu'en fait *il n'y a pas de libération d'histamine à la suite de la seconde injection de la substance histamino-libératrice*. Les dosages étant pratiqués après hydrolyse acide, il est difficile d'accepter l'hypothèse d'un conjugué du type histamine-héparine. Ceci exclut aussi l'hypothèse d'une « désensibilisation » des récepteurs à l'histamine. Bien

plus chez un animal devenu refractaire a un type de substances histamino-liberatrices on peut obtenir les effets habituels accompagnes d une augmentation de l histamine plasmatique a la suite de l injection d un histamino-liberateur appartenant a l autre groupe

De ce phenomene on peut suggerer l explication suivante a la suite de

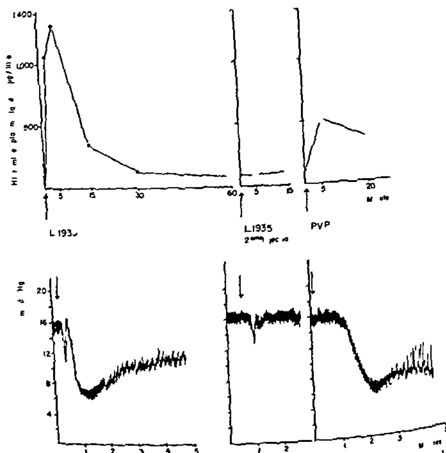


Fig 6 — Chien de 20 kg anesthesié avec du chloralose En bas enregistrement de la pression artériel e femorale En haut taux de l'histamine plasmatique A gauche l injection intraveineuse 1 mg/kg de 1935 L produit une baisse importante de la pression arterielle et une hyperhistaminemie importante Au milieu une deuxieme injection de la même dose de 3 mg/kg de 1935 L pratiquee 72 minutes apres la premiere est sans effet sur la pression artérielle Il n y a pas de libération d histamine A droite l injection de 1 ml/5 kg de polyvinylpyrrolidone à 25 p 100 pratiquée 30 minutes plus tard chez le même animal provoque une baisse importante de la pression artérielle et une libération d histamine

la premiere stimulation cellulaire par la substance histamino liberatrice il se produit un etat réfractaire de la cellule qui reste insensible pendant une certaine duree à l égard de cette substance ou d une substance voisine Cet

état d'insensibilité pourrait être dû à une combinaison chimique temporaire de certaines structures de la membrane ou du protaplasma avec la substance. Le même mécanisme peut être invoqué pour expliquer l'absence d'action de substances histamino-libératrices lorsqu'on les administre très lentement en perfusion veineuse.

L'impression se dégage que les deux groupes de substances histamino-libératrices n'exercent pas le même mode d'action. Avec les substances

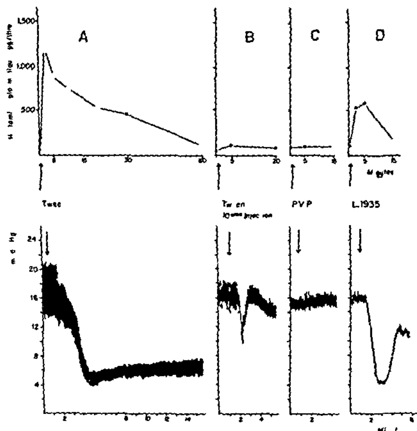


FIG. — Chien de 17 kg anesthésié avec du chloralose. En bas, enregistrement de la pression artérielle. En haut, taux de l'histamine plasmatique.

En A. Action de la première injection de tween 20 (0,25 cm³ d'une solution à 10/100 p. kg) : collapsus vasculaire et élévation importante de l'histamine plasmatique. Les injections sont poursuivies au rythme de deux par jour.

En B. Dixième injection de la même dose de tween 20 (0,25 cm³ d'une solution à 20/100 kg) : hypotension fugace, pas de libération d'histamine.

En C. 30 minutes après l'injection précédente, on injecte 0 cm³ par kg d'une solution à 25 p. 100 de la polyvinylpyrrolidone (P.V.P.). (Ce chien n'a jamais reçu auparavant de polyvinylpyrrolidone.) Pas d'hypotension, pas de libération d'histamine.

En D. 30 minutes après, on injecte 1 mg/kg de 1935 L : hypotension modérée et libération d'histamine.

plus chez un animal devenu réfractaire à un type de substances histamino libératrices, on peut obtenir les effets habituels accompagnés d'une augmentation de l'histamine plasmatique à la suite de l'injection d'un histamino libérateur appartenant à l'autre groupe

De ce phénomène on peut suggérer l'explication suivante à la suite de

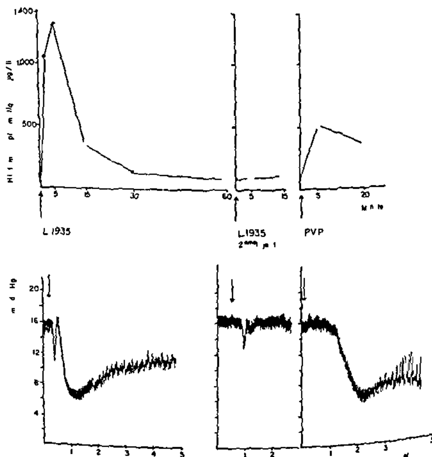


Fig 6 — Chien de 20 kg anesthésié avec du chloralose En bas enregistrement de la pression artérielle fémorale En haut taux de l'histamine plasmatique
A gauche l'injection intraveineuse 1 mg/kg de 1935 L produit une baisse importante de la pression artérielle et une hyperhistaminémie importante
Au milieu une deuxième injection de la même dose de 3 mg/kg de 1935 L pratiquée 72 minutes après la première est sans effet sur la pression artérielle Il n'y a pas de libération d'histamine
A droite l'injection de 1 ml/5 kg de polyvinylpyrrolidone à 5 p 100 pratiquée 30 minutes plus tard chez le même animal provoque une baisse importante de la pression artérielle et une libération d'histamine

la première stimulation cellulaire par la substance histamino libératrice il se produit un état réfractaire de la cellule qui reste insensible pendant une certaine durée à l'égard de cette substance ou d'une substance voisine Cet

etat d insensibilite pourrait etre du a une combinaison chimique temporaire de certaines structures de la membrane ou du protaplasma avec la substance Le meme mecanisme peut etre invoqué pour expliquer l absence d action de substances histamino libératrices lorsqu on les administre tres lentement en perfusion veineuse

L impression se degage que les deux groupes de substances histamino-liberatrices n exercent pas le meme mode d action Avec les substances

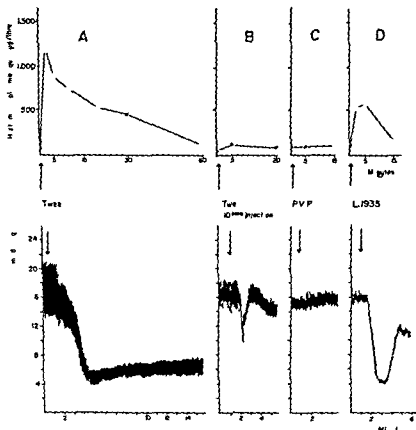


Fig 7 — Chien de 17 kg anesthesié avec du chloralose En bas enregistrement de la pression arterielle En haut taux de l histamine plasmatique

En A Action de la premiere injection de tween 20 (0 25 cm³ d une solution a 10 100 p kg) collapsus vasculaire et elevation importante de l histamine plasmatique Les injections sont poursuivies au rythme de deux par jour

En B Dixieme injection de la même dose de tween 20 (0 75 cm³ d une solution à 20 100 kg) hypotension fugace pas de libération d histamine

En C 30 minutes apres l injection précédente on injecte 0 2 cm par kg d une solution à 25 p 100 de la polyvinylpyrrolidone (P V P) (Ce chien n a jamais reçu auparavant de polyvinylpyrrolidone) Pas d hypotension pas de libération d histamine

En D 30 minutes apres on injecte 1 mg/kg de 1935 L hypotension modérée et liberation d'histamine

macromoleculaires le résidu d histamine tissulaire non liberable est plus eleve qu avec les amines basiques Chez le Chien les substances macro moleculaires exercent une action protectrice reciproque mais les animaux devenus refractaires aux substances macromoleculaires sont encore susceptibles de reagir aux amines basiques (fig 7) Le contraire est également vrai

Le meme probleme a eté étudié chez le Rat (32) Quatre substances histamino liberatrices le dextran l ovomucoide le 1935 L et le 48/80 ont été etudies chez cette espece animale quant a leur aptitude a provoquer une protection croisée reciproque Les tests choisis ont eté d une part la détermination de la dose seuil active sur la permeabilite capillaire cutanee et d autre part le taux de l hyperhistaminemie plasmatique après injection de ces substances

Les animaux traites par une des substances macromoleculaires deviennent refractaires aux autres substances du meme groupe, mais ils reagissent quasi normalement aux amines cycliques basiques telles que le 1935 L et le 48/80 Par contre si les animaux ont ete soumis a un traitement prolonge par une amine basique par exemple le 48/80 et ils sont devenus de ce fait refractaires a cette substance ceux ci ne réagissent plus ni aux amines basiques ni aux macromolécules

L explication de ce phénomene n est pas aisée Celle qui nous parait la plus plausible est la difference de lieu d action de ces substances Ainsi Nishiyama et ses collaborateurs (33) ont montre chez le Chien que le 48/80 libere principalement l histamine du foie et du muscle strié alors que la polyvinylpyrrolidone le tween et la sinomenine la detachent surtout de la peau et a bien moindre degre du foie et des muscles

C est parce que les substances histamino liberatrices suivant leur constitution chimique ne liberent pas l histamine des memes structures cellulaires qu elles ne parviennent pas a assurer une protection croisée complete et reciproque Ce probleme du siege d action de substances histamino liberatrices est directement lie a celui de l anaphylaxie

E SUBSTANCES HISTAMINO LIBÉRATRICES ET ANAPHYLAXIE

L interet de l emploi de substances histamino libératrices en relation avec les phénomenes anaphylactiques est bien évident Malgré un nombre important de recherches ce probleme n est pas entierement résolu Il y a plusieurs raisons a cela les histamino liberateurs n affectent que tres peu le Cobaye qui est l animal de choix pour l etude de l anaphylaxie D autre part le Rat albinos qui réagit remarquablement aux substances histamino liberatrices est un mauvais animal reactif pour l anaphylaxie L anaphylaxie revet chez cette espece animale une allure particulière et les antihistaminiques sont inefficaces contre le choc anaphylactique du Rat

Malgre ces difficultes on possede actuellement un certain nombre de donnees expérimentales qui montrent l existence d une protection croisee entre les substances histamino liberatrices et l anaphylaxie chez le Chien

Voici brievement resumés les résultats de recherches que nous avons realisees en collaboration avec M et M[me] Liacopoulos sur la protection

exercee par les substances histamino liberatrices contre le choc anaphylactique chez le Chien

Seize chiens ont été sensibilisés par l injection intrapéritoneale de sérum de cheval Apres trois semaines les animaux ont éte divises en deux groupes chez le premier groupe on a explore la sensibilisation anaphylactique sans aucun traitement préalable Les animaux ayant survecu au choc anaphylactique ont alors été soumis pendant neuf jours a un traitement avec une des substances histamino libératrices tween 20 ou 1935 L et eprouves de nouveau quant a leur sensibilite anaphylactique a la fin de ce traitement

Les animaux du second groupe ont ete soumis trois semaines apres la sensibilisation a un traitement par le 1935 L ou le tween 20 qui fut poursuivi durant neuf jours precédant l injection déchainante Tous les animaux de ce groupe ont éte repris après huit jours de repos et éprouvés de nouveau quant a leur sensibilité au sérum de cheval

Lors des injections déchainantes les animaux ont ete anesthesies avec du chloralose On a enregistre la pression artérielle et l histamine plasmatique a éte dosée également apres les injections du serum de cheval et des substances histamino libératrices par la methode de Code Les resultats sont resumes dans le tableau III

Les conclusions suivantes peuvent etre degagees de ces experiences

1° Tous les animaux sauf un ont réagi à l injection dechainante de serum de cheval par un choc grave Trois chiens ont succombe à la suite du choc anaphylactique

2° On ne constate pas toujours de relation évidente entre la gravite du choc mesuree par l importance de la baisse de la pression sanguine et le taux de l histamine plasmatique Chez trois chiens dont deux sont morts rapidement on a constate des taux d histamine s élevant jusqu a 6 000 μg/l Chez les autres l élévation de l histamine plasmatique ne depassait pas 150 à 200 μg l

3° Dans le groupe d animaux traites par le 1935 L un a ete protége completement deux ont fait un choc leger trois ont fait un choc sévère ou grave

4° Dans le groupe d animaux traités par le tween six ont éte entierement protéges et un seul a reagi par un choc sévere

Les resultats de ces expériences suggerent que les substances histamino libératrices macromoléculaires se montrent plus efficaces dans la protection du Chien contre le choc anaphylactique que les amines basiques Faut il conclure que le point d impact d action des substances macromoleculaires est le meme que celui du complexe antigene anticorps ? Autrement dit l histamine liberee au cours de la reaction anaphylactique provient elle des memes sources que l histamine mise en liberté par les substances macromoléculaires ? C est bien l impression qui se dégage de ces resultats

TABLEAU III

Protection contre le choc anaphylactique
par traitement préalable avec des substances histamino libératrices

Substance histamino libératrice	Numéro du chien	Injection déchaînante de contrôle: Importance de l'hypotension (Chiffres extrêmes en mm de Hg) Avant	Après	Histamine plasmatique (Chiffres extrêmes) Avant	Après	État du choc	Injection déchaînante après traitement préalable par substance histamino libératrice: Importance de l'hypotension (Chiffres extrêmes en mm de Hg) Avant	Après	Histamine plasmatique (Chiffres extrêmes) Avant	Après	État du choc
Néant	43[1]	160	30	60	3 013	+++++ mort					
	10[1]	140	27	13	6 187	+++++ mort					
	50[1]	160	60	35	100	+++++ mort					
I 1935	56[1]	145	60	68	195	++	140	125	72	108	±
	64[1]	170	45	80	86	++++	185	175	25	25	±
	4[2]	140	20	27	45	++++	170	50	15	30	+++
	55[2]	120	20			+++	180	40	35	114	++++
	59[2]	160	70	141	324	+++	180	120	42	82	++
	5[2]	160	60	30	120	+++	160	155	27	50	o
Tween 20	65[1]	200	30	68	156	++++	190	80	indos	36	+++
	63[1]	170	85	81	80	+++	210	10	15	71 5	o
	58[2]	100	20			+++	150	140	57	140	o
	57[2]	160	130	50	150	+	120	120	43	56	o
	48[2]	190	40	63	193	++++	150	140	37	50	o
	52[2]	130	30			++++	160	160	45	55	o
	8[2]	130	30	20	1 110	++++	120	115	25	77	o

1 *Groupe d'animaux n° 1*

Protocole type d'expérience

27 1 1958 injection sensibilisante de sérum de cheval
1 2 1958 nouvelle injection sensibilisante de sérum de cheval
24 2 1958 injection déchaînante de sérum de cheval (contrôle)
du 5 au 15 3 1958 injections intraveineuses journalières de Tween 20 ou de 1935 L
15 3 1958 injection déchaînante de sérum de cheval

2 *Groupe d'animaux n°*

Protocole type d'expérience

27 1 1958 injection sensibilisante de sérum de cheval
1 2 1958 nouvelle injection sensibilisante de sérum de cheval
19 3 au 1 3 1958 injections intraveineuses journalières de Tween 20 ou de 1935 L
1 3 1958 injection déchaînante de sérum de cheval
8 3 1958 injection déchaînante de sérum de cheval (contrôle)

+++++ choc mortel ++++ choc grave +++ choc sévère ++ choc moyen + choc léger ± choc douteux o pas de choc

F MISE EN LIBERTÉ D AUTRES MÉDIATEURS ENDOGÈNES PAR LES SUBSTANCES HISTAMINO LIBÉRATRICES

Les altérations brusques de la membrane cellulaire et des liaisons proto plasmiques que déterminent les substances histamino libératrices ainsi que la réaction antigène anticorps et dont l expression morphologique est l éclatement et la dégranulation des mastocytes a pour conséquence la

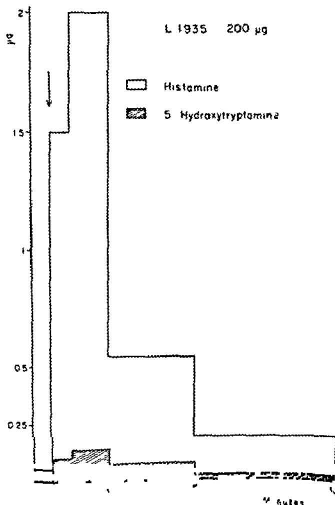


Fig 8 — Train postérieur de rat perfusé avec une solution de Ringer Locke A o minute en ↓ addition de 1935 L (200 µg) au liquide de perfusion il se produit une libération quasi immédiate d histamine et de 5 hydroxytryptamine

diffusion d autres substances emmagasinees sous forme inactive au sein de la cellule

Héparine On sait depuis longtemps, qu une de ces substances qui chez le Chien tout au moins accompagne l histamine lors du choc ana phylactique et peptonique est l héparine Bien que la diffusion de l héparine soit bien moins évidente meme chez le Chien lors de l emploi de substances histamino liberatrices y incluses les polymeres macromoleculaires une augmentation du taux de l héparine plasmatique parallele a celle de l hista mine a ete signalée par Mac Intosh et Paton (14) avec certaines amines basiques Il y a cependant a cet égard une difference notable avec le choc anaphylactique et peptonique dont l explication est a la fois malaisée et embarrassante

5 *hydroxytryptamine* on possede actuellement une série de preuves de la liberation simultanée de la 5 hydroxytryptamine par toute une série de substances histamino liberatrices 48/80 (34) 1935 L (35) dextran (35) La figure 7 qui est extraite de nos travaux personnels récents montre la cinetique de la liberation de l histamine et de la 5 hydroxytryptamine par le 1935 L lors de la perfusion du train posterieur de rat. Le role de la 5 hydroxy tryptamine dans la production des troubles cliniques dus a l injection de substances histamino liberatrices n est pas encore definitivement etabli Il parait cependant tres plausible que chez le Rat la 5 hydroxytryptamine soit en grande partie responsable de ces accidents Chez les animaux ayant subi une depletion de 5 hydroxytryptamine par un traitement avec la reserpine l injection de 48/80 entraine une mobilisation d histamine sans provoquer d œdeme des extrémités (36) Si l on compare l action de l hista mine et de la 5 hydroxytryptamine quant a leur abilite à provoquer par injection intracutanee le trouble local de la perméabilité capillaire et l œdeme la 5 hydroxytryptamine s avere etre environ deux cents fois plus efficace (37)

Parmi les antagonistes susceptibles d empecher les troubles cliniques provoqués par les substances histamino liberatrices le diéthylamide de l acide lysergique (LSD 25) la chlorpromazine et la prométhazine sont les plus actifs alors que les antihistaminiques plus spécifiques et notamment la mépyramine sont très peu efficaces (38 39) Si donc chez le Rat il se produit sous l effet de substances histamino libératrices une décharge concomitante d histamine et de 5 hydroxytryptamine on n a jamais mis en évidence de liberation de 5 hydroxytryptamine ni chez le Chien ni chez le Cobaye Chez ces deux especes animales l action de la 5 hydroxytryptamine est insignifiante et d apres nos essais tout récents l histamine semble etre le médiateur essentiel sinon exclusif des reactions anaphylactiques chez le Cobaye

Autres substances Paton (8) a signalé l apparition dans le sang de chien ayant reçu du 48/80 de la slow reacting substance qui on le sait produit une contraction progressive de l intestin et dont l effet n est pas neutralisé par les antihistaminiques de synthese Il est intéressant de rappeler ici que cette substance a pu etre décelée dans le sang des animaux au cours du choc anaphylactique (40) et dans le liquide de perfusion de poumon d animaux sensibilises apres addition de l antigene (41) La signification de cette substance est encore obscure

Le potassium plasmatique augmente apres injection de substances

histamino libératrices ou même de l'histamine (42). La diffusion du potassium doit être en relation avec les altérations de la perméabilité de la membrane cellulaire.

G. UTILISATION DES SUBSTANCES HISTAMINO-LIBÉRATRICES CHEZ L'HOMME

L'emploi de substances histamino-libératrices chez l'Homme revêt à la fois un intérêt pathogénique et un intérêt thérapeutique. L'intérêt pathogénique peut se résumer ainsi : peut-on réaliser chez l'Homme par l'emploi de substances histamino-libératrices des syndromes cliniques qui sont similaires sinon identiques aux affections spontanées ?

L'injection intradermique de 48/80 (43) ou de 1935 L (44) provoque chez l'Homme une réaction érythémato-papulaire prurigineuse tout à fait similaire à celle produite par l'histamine. La répétition des injections locales au même point conduit à l'extinction de la réaction.

L'administration de 0,1 mg p. kg de 1935 L par voie veineuse (45, 46) à un sujet exempt de troubles allergiques provoque un tableau symptomatique très caractéristique : une à deux minutes après l'injection, le malade accuse des picotements généralisés, particulièrement intenses sur le visage et le thorax. La peau se couvre d'érythème, elle devient chaude et prurigineuse. L'érythème est plus intense sur le visage et le thorax que sur les jambes. Le pouls s'accélère et sa fréquence peut atteindre 120 à 150 pulsations par minute. Le malade ressent des battements d'artères dans les tempes. Une céphalée soudaine accompagne souvent ces phénomènes. La tension artérielle baisse de 2 à 4 cm de Hg d'une manière passagère ; parfois on note une faible élévation de celle-ci. Une augmentation de la sécrétion gastrique complète le tableau.

Le dosage d'histamine plasmatique révèle une brusque augmentation du taux de l'histaminémie qui peut s'élever de 50 µg/l à 500-600 µg/l. Tous ces phénomènes sont éminemment fugaces et disparaissent après cinq à dix minutes.

Si la dose administrée est plus élevée, les symptômes décrits revêtent une allure plus sévère (45). On peut alors noter en outre une baisse intense et prolongée de la pression artérielle avec malaise ou même collapsus. On peut aussi voir apparaître des plaques urticariennes sur le corps.

Fort différent est le tableau clinique chez un individu allergique. Prenons à titre d'exemple un sujet atteint d'urticaire même potentielle : les symptômes immédiats sont les mêmes que chez un sujet normal. Mais alors que chez le sujet normal tous les symptômes se dissipent dix à quinze minutes après d'une manière définitive, l'urticarien va présenter une seconde phase caractérisée par l'apparition d'une crise violente d'urticaire. En voici l'évolution clinique : dès la disparition de la vague érythémateuse et des picotements qui suivent l'injection de 1935 L, le sujet urticarien accuse une sensation de prurit sur le visage, le cuir chevelu, le thorax, etc. C'est alors qu'on voit apparaître au niveau des glandes sudoripares des élevures d'abord ponctiformes qui rapidement s'étendent et fusionnent pour former des plaques urticariennes rouges surélevées de contours irréguliers et forte

ment prurigineuses La distribution de ces plaques d urticaire souvent véritablement geantes est irreguliere et predomine en general sur le thorax les bras et l abdomen Mais elles peuvent affecter tout le corps Nous avons souvent note un œdeme de la nuque du front ou de la bourse Un sentiment de malaise genéral accompagne ces symptomes sans qu il y ait le moindre symptome alarmant Ces troubles persistent suivant les cas trente minutes a deux heures et se dissipent lentement

Le fait important est que la répétition des injections matin et soir mene rapidement vers l installation d un etat refractaire et dans ces conditions, l injection de 1935 L meme a des doses plus élevees reste pratiquement sans effet L état réfractaire peut persister quelques jours apres ce delai l individu reagit de nouveau a la substance par les memes symptomes

Chez un asthmatique l injection de la substance histamino liberatrice provoquera une crise d asthme et pas ou peu d urticaire

Chez un individu sujet a des migraines c est une crise typique de céphalee migraineuse qui suivra l injection de la substance

Ainsi l administration d une substance histamino libératrice est capable de déclencher chez un sujet meme potentiellement allergique le tableau clinique typique de la maladie spontanée

Comment interpréter ces faits ? Faut il admettre que les individus allergiques liberent plus d histamine que les non allergiques ? Cette hypothese ne peut pas etre retenue car les taux d histamine plasmatique trouves chez les sujets urticariens apres injection de la meme dose de 1935 L sont plutot inferieurs à ceux trouvés chez les sujets de controle S agit il d un trouble de liberation d histamine au niveau de l organe de choc ou bien d une sensibilite plus grande des recepteurs au niveau de l organe de choc C est possible mais actuellement rien ne permet de l affirmer

Signalons toutefois que l administration préalable d un antihistaminique de synthese empeche totalement l apparition des symptomes cliniques provoqués par la substance histamino liberatrice à l exception de l hypersécrétion gastrique

Telles qu elles sont aujourd hui ces observations présentent un intéret pathogenique evident et on peut présumer que les travaux actuellement poursuivis enrichiront et étendront nos connaissances dans ce domaine

Quels sont les resultats thérapeutiques obtenus avec les substances histamino-liberatrices ? Il n y a encore que tres peu de renseignements sur ce point Nous avons traite quinze cas d urticaire trois cas d eczema diathesique deux cas de migraine par des injections répétées de 1935 L Dans l urticaire nous avons observe dans tous les cas une amélioration clinique durant le traitement Lorsque le malade est devenu refractaire au 1935 L les crises spontanées d urticaire meme apres exposition se sont atténuées ou ont disparu Cette am lioration n etait en général que de courte duree Le plus souvent quelques jours apres l arret du traitement les symptomes habituels ont reapparu Dans quelques cas l amelioration semblait persister plus longtemps mais il est difficile de connaitre et d affirmer la part due au traitement dans cette amelioration clinique Dans les autres cas les résultats etaient peu consistants

Il ne semble donc pas que les produits actuellement disponibles puissent etre utilisés avec succes en thérapeutique humaine Disons toutefois que

malgre l apparence dramatique des symptomes declenches nous n avons jamais eu à déplorer ni meme a craindre un accident grave mettant la vie du malade en danger

II MÉCANISME D ACTION DES SUBSTANCES HISTAMINO LIBÉRATRICES

Un phenomene physiologique d une telle ampleur et d une telle importance ne pouvait pas ne pas stimuler la curiosité et la sagacite des physiologistes et des biochimistes A l heure actuelle de nombreuses hypotheses explicatives ont ete proposées et leur nombre indique clairement qu aucune d elles n est reellement satisfaisante

Il est certain que l administration de substances histamino liberatrices provoque une altération morphologique de certaines populations cellulaires et notamment des mastocytes (47) Une étude microscopique soigneuse a revélé que la cellule mastocytaire expulse de son sein des granulations basophiles metachromatiques sans que la cellule elle meme soit detruite En effet durant les jours qui suivent on voit apparaitre à l intérieur du protoplasma de ces cellules de nouvelles granulations *régénérées* Le mécanisme par lequel ces granules proportionnellement enormes traversent la membrane cellulaire sans endommager la cellule reste mysterieux La plupart des auteurs considerent a l heure actuelle que la libération d histamine est en rapport avec les modifications morphologiques des mastocytes La teneur exceptionnellement élevée de ces cellules en histamine rend plausible une telle hypothese (5 49) D autre part le fait que les cellules mastocytaires contiennent egalement des taux eleves d héparine (50) de 5 hydroxytryptamine (51) les deux substances libérees souvent simultanement avec l histamine renforce considérablement cette hypothese En allant plus loin dans cette voie Mac Intosh et Paton (14) pensent que l histamine est rattachee par des forces ioniques au radical acide de l heparine ou meme des acides ribonucleiques sous forme de complexes insolubles Les substances histamino libératrices agiraient en deplaçant l histamine de cette liaison Il y a lieu de dire que cette hypothese aussi seduisante qu elle puisse paraitre possede de nombreuses et graves lacunes On peut dire qu elle ne satisfait pas les auteurs eux memes qui en connaissent les imperfections Nous ne citerons ici que quelques objections grossieres une molécule de 48/80 peut liberer jusqu à 10 à 20 molecules d histamine cette constatation ne peut s expliquer par un simple deplacement ionique Le complexe histamine heparine ou histamine acide ribonucleique n est pas toujours precipitable alors que le meme complexe forme avec les histamino libérateurs se presente comme un gros precipite Pour libérer l histamine de ses attaches protoplasmiques il faut admettre que la substance histamino liberatrice entre dans la cellule si pour certaines amines simples cette possibilité peut à la rigueur etre concevable il n en est guere de meme pour certains ammoniums quaternaires Comment expliquer enfin l effet des substances macromoléculaires qui selon toute vraisemblance ne quittent meme pas le lit vasculaire? La meme question est valable pour ce qui est du complexe antigene anticorps Le probleme reste donc entier

Pour ce qui est des autres hypotheses nous ne ferons que les mentionner

pour les écarter Une augmentation du taux de l histamine par une inhibition par les substances histamino libératrices de l activité des enzymes histaminolytiques n est pas à retenir pour des raisons evidentes

Une autre theorie émise (52) est que les substances histamino libératrices activeraient les proteases seriques telles que la fibrinolysine Cette conception se heurte aux memes difficultes que la theorie de la libération d histamine par les ferments proteolytiques

On peut dire que la difficulté centrale et actuellement insurmontable, reside dans l ignorance de la forme biochimique de l histamine intra cellulaire Aussi longtemps que ce probleme fondamental ne sera pas résolu les tentatives d ameliorer nos connaissances sur le mecanisme de libération de l histamine soit par des substances chimiques simples soit par la reaction antigene anticorps ont bien peu de chances d etre couronnees de succes

RÉSUMÉ

On trouve chez le mammifere (Rat albinos) 20 a 30 mg d histamine par kg La teneur des divers tissus en histamine est tres variable chez le Rat l organe de beaucoup le plus riche est le tegument cutane viennent ensuite par ordre decroissant avec des taux bien plus faibles le muscle strié le tube digestif le foie le poumon

Le probleme crucial demeure la forme biochimique de l histamine cellulaire L histamine preexiste dans les cellules sous forme d un precurseur inactif D apres les theories récentes elle s y trouverait fixee aux structures protoplasmiques (mitochondries) par une simple liaison ionique Cette théorie ne permet pas d expliquer comment l histamine est libérée au cours de la reaction anaphylactique

L introduction de substances histamino libératrices a contribue à élargir nos connaissances dans ce domaine

Apres avoir esquisse une classification de substances histamino libératrices l auteur étudie les conditions la cinetique et les modalités de la libération de l histamine chez l animal et l homme

Le fait que l hypothermie n empeche nullement la libération de l histamine par le 48/80 ou le 1935 L mais inhibe totalement celle causee par le dextran indique que le mécanisme d action de diverses substances histamino libératrices n est pas identique

L état réfractaire acquis apres une injection unique de l histamino liberateur doit etre distingue de l etat refractaire du a l epuisement de l histamine tissulaire

La protection croisee reciproque que conferent les diverses substances histamino libératrices depend de leur structure physico chimique A l egard du choc anaphylactique du Chien la protection obtenue avec les substances macromoleculaires se révele plus efficace que celle acquise avec les amines basiques

Chez l Homme les substances histamino libératrices produisent un syndrome histaminoide typique Chez les sujets allergiques ces troubles sont suivis d une éclosion souvent dramatique des symptomes de la maladie

allergique spontanée dont le malade est atteint La répétition des injections de la substance histamino libératrice conduit à l'installation d'un état réfractaire et à l'extinction plus ou moins prolongée des symptômes morbides cliniques

L'intérêt de l'emploi clinique des substances histamino libératrices et leur mécanisme d'action sont discutés

SUMMARY

Twenty to thirty mg per kg of histamine is the quantity found in mammals (albino rats) inequally distributed in the various tissues In this animal species the skin contains the largest amount of histamine while much smaller quantities are found in the striated muscles the digestive tract the liver the lungs etc

The biochemical form of the cellular histamine remains still the crucial problem Histamine is present in the cells as an inactive precursor According to the recent theories histamine is linked to the protoplasmic structures (mitochondria) by a simple ionic bond However this conception does not explain the release of histamine in anaphylactic reactions

The recent introduction of the histamine liberators has greatly contributed to the extension of our knowledge in this domain

After having outlined a classification of the histamine liberators the author studies the conditions the kinetics and the patterns of the histamine release in animal and man Hypothermia which does not affect at all the release of histamine by 48 80 and 1935 L prevents more or less completely the liberation of histamine by macromolecular substances such as dextran This suggests a different mechanism of actions of the two groups of histamine liberators The refractory state is due to a different mechanism when it appears after a single injection or after a prolonged and repeated treatment which leads to the depletion of the tissular histamine The efficiency of the crossed protection obtained with the various histamine liberators depends on the physico chemical nature of the substance As to the anaphylactic shock in dogs the macromolecular substances are more efficacious than the basic amines

In man the histamine liberators produce a very characteristic histaminic syndrome In allergic patients these troubles are followed by a dramatic bursting out of the symptoms of the spontaneous allergic disease

The repetition of the injections of histamine releasing substances leads in man also to a refractory state and to a more or less prolonged disappearance of the clinical symptoms of the disease The value of the histamine liberators in clinical use and their mechanisms of action are discussed

ZUSAMMENFASSUNG

Reihenfolge ihrer Verminderung von dem quergestreiften Muskel dem Verdauungskanal der Leber und der Lunge

Das Hauptproblem bleibt die biochemische Form des zellularen Histamins Das Histamin ist in der Zelle in Form einer inaktiven Vorstufe vorhanden Nach den jungsten Theorien ist diese Vorstufe an Protoplasmastrukturen (Mitochondrien) mittels einer einfachen Ionenbindung fixiert Diese Theorie erlaubt aber keine Erklarung wie das Histamin im Verlaufe der anaphylaktischen Reaktion freigesetzt wird

Die Einfuhrung von histaminfreisetzenden Substanzen hat unser Wissen auf diesem Gebiet vertieft

Nachdem der Autor eine Einteilung der histaminfreisetzenden Substanzen skiziert hat studiert er die Bedingungen die Kinetik und die Art und Weise der [illegible]

Die Tatsache [illegible]
48 80 oder 1935 [illegible]
zeigt dass der Wirkungsmechanismus der verschiedenen histaminfreisetzenden Substanzen nicht identisch ist

Der Refraktarzustand nach einer einzigen Injektion einer histaminfreisetzenden Substanz muss von jenem Refraktarzustand unterschieden werden *der durch eine Erschopfung des Gewebshistamins bedingt ist*

Der reziproke Kreuzschutz der verschiedenen histaminfreisetzenden Substanzen hangt von ihrer physikalisch chemischen struktur ab Hinsichtlich des anaphylaktischen Schockes beim Hund zeigt sich der mittels makromolekularer Substanzen erzielte Schutz als viel wirksamer als der mit Aminbasen erzeugte

[illegible]
his [illegible]
Stc [illegible]
einer allergischen Spontanerkrankung an der Kranke laboriert Wiederholte Injektionen der histaminfreisetzenden Substanz fuhrt zum Auftreten eines Refraktarzustandes und zu einem mehr oder weniger langen Verloschen der klinischen Krankheitssymptome

Die Moglichkeit einer klinischen Abwendung der histaminfreisetzenden Substanzen und ihr Wirkungsmechanismus werden diskutiert

RESUMEN

La cantidad de histamina presente en los mamiferos (ratas albinas) es de 20 a 30 mg por kilogramo de animal distribuida diferentemente en los tejidos En esta especie animal la mayor cantidad se encuentra en la piel en tanto que los musculos estriados el aparato digestivo el hígado los pulmones etc contienen una proporción mucho menor

La histamina se encuentra en las células en estado de precursor inactivo en una forma bioquímica cuyo conocimiento constituye todavia el problema crucial De acuerdo a las terías mas recientes está unida a las estructuras protoplasmáticas (mitocondrios) por una simple union iónica pero no obstante esta concepción no explica la liberación de histamina durante la reaccion anafilactica Los estudios realizados con las sustancias liberadoras de histamina han contribuido de manera importante a aclarar muchos aspectos

El autor luego de una somera clasificación de los liberadores de histamina

se refiere a las condiciones la cinética y las modalidades de la liberacion en los animales y en el hombre La hipotermia que no afecta la liberación de histamina producida por el 48/80 o el 1935 L inhibe la acción de las sustancias macromoleculares como el dextran lo cual sugiere un distinto mecanismo de acción en ambos casos El mecanismo por el cual se llega a un estado de refractoriedad es diferente segun que sea producido por una sola inyección o por un tratamiento prolongado que causa un agotamiento de la histamina contenida en los tejidos La eficiencia de la proteccion cruzada obtenida con varios liberadores depende de las caracteristicas fisicoquímicas de cada uno de ellos En lo que respecta al shock anafilactico en el perro las sustancias macromoleculares son más activas que las aminas básicas

En el hombre los liberadores de histamina producen un sindrome «histamínico» bien tipico En los enfermos alergicos los trastornos son acompanados de una dramática recidiva de los sintomas de su alergia espon tánea

Las inyecciones repetidas de liberadores de histamina producen tambien en el hombre un estado de refractoriedad y una desaparicion mas o menos durable de los sintomas clinicos

El autor se refiere y discute el valor de estas sustancias en la terapeutica y el mecanismo por el cual actuan

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LE POUVOIR HISTAMINOPEXIQUE DU PLASMA SANGUIN CHEZ L'HOMME NORMAL ET CHEZ L'HOMME ALLERGIQUE

par

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Sous le nom de pouvoir histaminopexique nous avons decrit en 1952 la propriété que possedent certaines humeurs de fixer *in vitro* une fraction de l'histamine qui leur est ajoutee

Au cours de nos recherches les faits suivants ont ete notamment constates

a) chez l'homme normal le plasma sanguin est doue de pouvoir histaminopexique et celui ci est de 30 p 100 environ

b) chez l'homme allergique le plasma sanguin est dépourvu de pouvoir histaminopexique

c) chez ce dernier nous avons pu faire apparaitre pour un temps un pouvoir histaminopexique de valeur normale pendant ce temps les crises allergiques ont cesse

Tels sont les trois points qui seront developpes dans ce rapport (*)

(*) Ces résultats ont été acquis par le travail de toute une équipe M[lle] Cl Laborde qui collabora dès l'origine à ces recherches n'a jamais cessé de contribuer à leurs développements expérimentaux cliniques et thérapeutiques dès le début D A Urquia y a participé à la suite de ses travaux sur le test de protection du Cobaye contre l'histamine M[me] Mordelet Dambrine a étudié le rôle des ions minéraux et a appliqué l'ultrafiltration à l'étude de l'histaminopexie J Thouvenot et M[me] N Flavian ont mis au point une *méthode colorimétrique* qui permet d'examiner comment varie l'histaminopexie selon les conditions du milieu M[me] N Flavian utilise en outre de l'histamine marquée au C^{14}

L'étude du pouvoir histaminopexique chez l'*Homme* n'a pu être menée à bien que grâce à la collaboration de nombreux services hospitaliers de Paris que nous regrettons de ne pouvoir tous mentionner ici qu'il nous soit du moins permis de remercier notre ami le Pr Charles Debray dans le service duquel nous avons pu étudier l'ulcère gastrique ou duodénal la recto-colite hémorragique et divers types d'allergie

I. L'HISTAMINOPEXIE PLASMATIQUE INNÉE

A. Techniques

Aucune précaution spéciale n'est requise pour la prise de sang : il n'est pas nécessaire que le sujet soit à jeun. On prélève habituellement 5 ml de sang environ, mais 2 à 3 ml peuvent suffire. La mesure peut se faire sur le sérum ou sur le plasma. Dans ce dernier cas on utilisera l'héparine en employant le minimum de cette substance capable d'éviter la coagulation.

a) *TECHNIQUE PHARMACOLOGIQUE*

Le sérum (ou le plasma) est soumis à une dialyse de 24 h sur eau physiologique (*) à la température du laboratoire. Cette opération est nécessaire pour éliminer les substances diffusibles qui pourraient exercer une action sur le test biologique.

Le lot d'expérience préparé dans du liquide de Tyrode non glucosé (**)

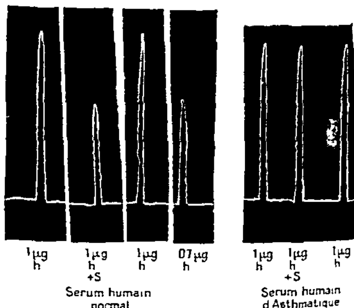


FIG. 1. — Le pouvoir histaminopexique du sérum humain. Sa disparition chez l'asthmatique.

Sérum humain dialysé pendant 24 heures sur une solution de ClNa à 9 p. 1 000. Les lots contiennent soit le dichlorhydrate d'histamine seul (h), soit ce même sel en présence du sérum dilué à 1/20 (h + S). On voit que le pouvoir histaminopexique de ce sérum humain normal est de 30 p. 100 et que celui de ce sérum d'asthmatique est nul.

(*) 1 ml de plasma sur 150 ml d'eau physiologique changée trois fois par 24 h.

(**) Composition p. 1000 : NaCl 8 ; $CaCl_2$ 0,2 ; KCl 0,2 ; $MgCl_2$ 0,1 ; $HNaCO_3$ 1. L'absence de glucose est recommandée pour éviter les contractions spontanées de l'intestin. Néanmoins, dans certains cas, on peut ajouter du glucose à 0,25 p. 1000.

contient le sérum sanguin à la concentration de 5 p. 100 et le dichlorhydrate d'histamine à la concentration de 10 (*).

Le test est l'iléon terminal de Cobaye ; l'organe baigne dans du liquide de *Tyrode non glucosé* ; le bain *maintenu à 37° subit un barbotage d'air* ; l'intestin est relié à un myographe isotonique qui exerce sur lui une tension comprise entre 2 et 3 g.

On essaie alternativement le lot d'expérience et la solution contenant l'histamine à la même concentration mais en milieu uniquement salin ; on constate alors régulièrement que l'histamine se montre moins active en présence du sérum sanguin et les contractions successives ainsi obtenues dessinent une image caractéristique en dents de scie (fig. 1). Naturellement on aura choisi pour de tels essais une concentration d'histamine qui se place dans la zone de plus grande sensibilité différentielle. Si l'on utilisait une concentration supramaximale, le phénomène ne pourrait se manifester.

Il s'agit ensuite de mesurer le pouvoir histaminopexique. Si la concentration de l'histamine mise en présence du plasma est représentée par 1, la concentration qui, dans le milieu uniquement salin, exerce la même action est par exemple de 0,7 (v. fig. 1). Dans ce cas, la présence du plasma a fait perdre à l'histamine 30 p. 100 de son activité ; on dira que le pouvoir histaminopexique de ce plasma est de 30.

Cette technique pharmacologique (M^{lle} Laborde, Parrot et Urquia 1953) a été adoptée par de nombreux auteurs. On peut la considérer présentement comme la technique de routine. Elle a permis maintes confirmations.

b) *TECHNIQUES PERMETTANT DE SÉPARER L'HISTAMINE LIBRE*

Le procédé pharmacologique permet en somme d'évaluer la concentration de l'histamine libre par son action biologique. Mais on peut se proposer de séparer cette phase libre par un procédé physique. On ajoute de l'histamine au plasma ou au sérum, puis on le soumet à la dialyse ou à l'ultrafiltration. On dose l'histamine de part et d'autre de la membrane et l'on constate alors qu'une part de l'histamine est retenue par les molécules non diffusibles du plasma.

1. Équilibre de dialyse

a) *Dosage biologique de l'histamine*

Voici à titre d'exemple le protocole d'un essai (Parrot, Urquia et M[lle] Laborde 1951).

La solution de dichlorhydrate d'histamine se trouve à la même concentration (100 µg/ml) de part et d'autre de la membrane de collodion dans du liquide de Tyrode ; le bain intérieur est de 5 ml ; le bain extérieur, d'un volume total de 10 ml, contient 2 ml de sérum humain normal. Au bout de 2 h 30, une fraction importante de l'histamine s'est déjà déplacée vers le compartiment extérieur ; celui-ci en effet contient alors 110 µg du sel d'histamine par ml, l'autre n'en contient plus que 70 µg. Tout se passe comme si

(*) Selon la sensibilité du test, on pourra utiliser une concentration d'histamine un peu différente, sans que l'évaluation du pouvoir histaminopexique se trouve sensiblement modifiée. Il s'agit naturellement ici de concentration en poids par volume et non de concentration moléculaire.

l histamine existait sous une phase libre de part et d autre de la membrane et qu en plus une fraction restait retenue du coté du serum

Dans ce premier exemple l histamine a ete dosee par la methode biologique Pour que ce dosage soit correct il faut annuler le pouvoir histaminopexique du plasma pour cela il suffit de diluer cent fois le milieu

b) *Dosage colorimetrique de l histamine* — On peut observer le phenomene sans recourir a aucun test biologique Il suffit de doser l histamine par une technique colorimetrique (Parrot Mme Flavian et Thouvenot 1957)

La solution de dichlorhydrate d histamine se trouve a la meme concentration (50 μg/ml) de part et d autre de la membrane de collodion, dans une solution de NaCl a 9 p 1000 en outre le compartiment interieur contient les globulines d un serum humain normal (2 μg/ml) les deux compartiments ont reçu le meme volume de liquide (7 5 ml) La dialyse dure 4 h Pendant ce temps l appareil est soumis a une agitation lente et continue Puis l histamine est dosee par la technique colorimetrique de Rosenthal et Tabor, telle qu elle a ete precisee par Thouvenot Mme Flavian et Weber (1957) On constate alors que dans tous les cas (16 essais) l histamine s est deplacee vers les globulines sa concentration peut etre devenue deux fois plus forte dans le compartiment qui a reçu les protéines plasmatiques que dans l autre

c) *Dosage spectrophotometrique de l histamine* — A la suite d equilibres de dialyse Klamerth (1955) dose l histamine au spectrophotometre à 2 115 Å et constate que cette substance se lie aux gamma globulines comme nous l avions précédemment etabli

d) *Mesure de la radioactivite (histamine marquee au C^{14})* — A la suite de nos experiences Kaplan et Davis (1953) ont etabli quelques equilibres de dialyse avec de l histamine marquee au C^{14} Le bain interieur contenait du serum humain ou une fraction de plasma humain apres avoir mesure la radioactivite uniquement dans le bain exterieur les auteurs conclurent qu il n y avait pas eu deplacement d histamine Cette conclusion ne repose que sur l etude de deux serums humains (*) Les auteurs ont meme neglige de s assurer que ces deux serums etaient bien doues de pouvoir histaminopexique Quant a la fraction II de Cohn que ces auteurs ont employee (*) nous avons eu plusieurs fois l occasion d observer qu elle perdait en vieillissant la propriete de fixer l histamine

En collaboration avec P Bonet Maury Mme Flavian et Mme Frovost nous avons egalement utilise l histamine marquee par le C^{14} (**) Le pouvoir histaminopexique des serums etait mesure au prealable et seuls etaient retenus ceux qui captaient au moins 30 p 100 (technique pharmacologique) Les equilibres de dialyse etaient conduits dans les memes conditions generales que precedemment (voir b) Les mesures de la radioactivite β due au C^{14} etaient faites a la fois sur le bain interieur et sur le bain exterieur de maniere qu un bilan puisse etre etabli Dans ces conditions d experience on observe un déplacement de l histamine radioactive vers les proteines plasmatiques et la difference est du meme ordre que celle qui avait pu etre notée avec les autres techniques de dosage (biologique et colorimétrique)

2 ULTRAFILTRATION — Si l on ajoute de l histamine a du plasma humain

(*) Communication personnelle

(**) Nous voulons adresser ici à R W S Hayer nos très vifs remerciements pour l histamine marquée qu il a eu la très grande courtoisie de nous faire parvenir

normal et qu'on le soumette ensuite à l'ultrafiltration (membrane de collodion sous une pression de deux atmosphères), on constate qu'une fraction de l'histamine ne traverse pas l'ultrafiltre (voir tableau IV) (recherches inédites avec Mme Mordelet-Dambrine).

c) *MODIFICATION DU SPECTRE D'ABSORPTION DE L'HISTAMINE*

Une liaison de l'histamine avec les protéines doit se manifester par une *modification de son spectre d'absorption*. Or, en effet, si l'on établit le spectre d'absorption de l'histamine dans le domaine de l'ultraviolet, on observe que la courbe se déforme et que le maximum se déplace lorsqu'on ajoute de la sérumalbumine au milieu (Klamerth, 1955).

B. Résultats

Ainsi, l'histamine n'exerce pas la même activité biologique selon que le liquide de Tyrode dans lequel elle est dissoute contient ou non du sérum humain normal préalablement dialysé. C'est sous cet aspect pharmacologique que le phénomène s'est d'abord présenté à nous. Trois possibilités furent examinées à cette époque :

1° Le test est devenu moins sensible à l'histamine ;
2° Une partie de l'histamine a été détruite ;
3° Une partie de l'histamine a été liée sous une forme inactive.

a) *NATURE DU PHÉNOMÈNE*

Aujourd'hui les résultats expérimentaux concordent pour montrer qu'il s'agit d'une captation. Les expériences d'équilibre de dialyse sont particulièrement démonstratives à cet égard : le déplacement de l'histamine ne s'observe que si le sérum utilisé est capable, dans les conditions de la technique pharmacologique, de diminuer l'activité de l'histamine. Bien plus, le sérum de *certains sujets allergiques augmente l'activité pharmacologique* de l'histamine ; or lorsque de tels sérums sont introduits dans un équilibre de dialyse, on constate qu'ils repoussent l'histamine. Ainsi il y a parallélisme entre les propriétés physico-chimiques des sérums et leurs effets pharmacologiques. En somme, la distribution spatiale des molécules d'histamine est homogène dans une solution purement saline ; elle peut devenir hétérogène lorsqu'on introduit dans ce milieu certaines molécules protéidiques.

Lorsqu'une molécule diffusible se déplace dans un milieu contenant des molécules non diffusibles, il y a lieu d'examiner d'abord s'il ne s'agit pas d'un banal équilibre ionique de type Donnan. Il semble bien qu'il n'en soit rien ici puisque, selon la nature du plasma, le déplacement de l'histamine se fait dans un sens ou dans l'autre ou ne se fait pas. De même Klamerth (1955) estime que, dans ses expériences, le rôle de l'effet Donnan est négligeable.

b) *CONDITIONS D'OBSERVATION*

1. LE FACTEUR TEMPS. — La captation de l'histamine est totale dès les premières secondes de contact ; c'est ce que permet de constater la technique pharmacologique. Pendant les deux ou trois heures qui suivent, rien ne vient modifier le phénomène. Il est évident que, dans les expériences de dialyse, le délai nécessaire pour observer pleinement le phénomène tient non à

la captation elle meme mais au temps qu il faut pour que la phase libre s equilibre de part et d autre de la membrane

2 CONDITIONS DE CONCENTRATION — *a*) Lorsque la captation de l histamine a ete constatee dans les conditions standardisees pour la technique pharmacologique il suffit de diluer le lot d expérience pour voir reparaitre un pourcentage important de l activité biologique disparue Par exemple dans les conditions habituelles le tube a essai contient dissous dans du liquide de Tyrode le serum à 5 p 100 et le dichlorhydrate d histamine a 10^{-6} la captation est de 35 p 100 environ Si l on dilue 10 fois ce lot dans le liquide de Tyrode la captation n est plus que de 5 p 100 environ (Parrot Urquia et M^lle Laborde 1952)

b) Si dans les tubes a essai l on maintient constante la concentration d histamine (dichlorhydrate 10^{-6}) et si l on abaisse la concentration du plasma humain le pouvoir histaminopexique evalue par la methode pharmacologique s annule lorsque la concentration du plasma tombe environ à 10^{-4} (Parrot M^lle Laborde et M^me Mordelet Dambrine 1958) (V tableau I)

TABLEAU I

Valeur du pouvoir histaminopexique du serum humain normal

Concentrat on du pl sma	5×10 [illegible]	5×10 [illegible]	5 [illegible] 10 [illegible]
Pouvoir histaminopexique moyen en p 100	30	20	5

c) Si l on maintient constante la concentration des proteines plasmati [illegible] hydrate d his [illegible] leve et [illegible] suivie de dosages colorimétriques travail inedit avec M^me Flavian)

3 CONDITIONS DE *p*H — Une etude est en cours avec M^me Flavian sur l influence du *p*H (dialyse puis colorimétrie) Les premiers resultats indiquent que la captation est au moins aussi importante au *p*H 6 qu a la neutralite mais qu elle est beaucoup plus faible a *p*H 8 4 et 9

4 SPÉCIFICITÉ DU POUVOIR DE CAPTATION ET INHIBITION COMPÉTITIVE — Les protéines du plasma sont capables de fixer un grand nombre de substances Mais la specificite de l histaminopexie pose un probleme beaucoup plus precis On peut le definir par trois critères

a) La proteine histaminopexique peut elle fixer d autres substances ?

b) Ces autres substances sont elles capables d inhiber l histaminopexie par competition ?

c) Ces autres substances sont elles incapables d etre fixées par un plasma depourvu de pouvoir histaminopexique ?

Nous ne pouvons presentement fournir à ces questions que des reponses partielles

— La technique pharmacologique ne nous a permis aucune conclusion en ce qui concerne l éventuelle captation de la putrescine du potassium

ou de l adrenaline l acetylcholine par contre semblerait se comporter comme l histamine (ileon isole de Cobaye)

— La captation de l histamine par le plasma sanguin etudiee par la technique pharmacologique se trouve diminuee par la présence dans la solution de dichlorhydrate de putrescine a la concentration de 25×10^{-4} c est une concentration tres inferieure a celle qui permet d obtenir une action propre de cette substance sur le test L histaminopexie est supprimee par l addition au lot d experience de dichlorhydrate d histidine a la concentration de 10^{-3} (Mlle Laborde)

Ainsi il parait des maintenant probable que la molecule histaminopexique est capable de fixer d autres petites molecules telles que l histidine l acetylcholine la putrescine

c) *FACTEURS CHIMIQUES*

1 MOLÉCULES HISTAMINOPEXIQUES — Si l on considere les protides separes du plasma et debarrasses des éléments minéraux qui les accompagnent normalement on constate que deux fractions sont capables de capter l histamine il s agit de la fraction gamma globuline et de la serumalbumine Ceci résulte aussi bien de la technique pharmacologique que de l equilibre de dialyse (Parrot Urquia et Mlle Laborde 1951 Parrot et Mlle Laborde inédit Idlamerth 1955)

a) *La fraction gamma globuline*

Nous avons tout d abord localise l activite histaminopexique dans les globulines telles qu on les obtient apres les avoir précipitees par le sulfate d ammonium à demi saturation Puis nous avons pu preciser que cette activite appartenait a la fraction II de Cohn il s agit donc d une gamma globuline Enfin des recherches en cours poursuivies en collaboration avec Sandor nous montrent que la molécule histaminopexique ne constitue qu un pourcentage extremement faible des gamma globulines elle est comprise dans la fraction gamma pseudo globuline qui est entrainee par le precipité d alpha euglobuline et de beta euglobuline par dilution du plasma au 1/15 avec de l eau distillee à pH 5 2 Ce procéde nous permet d obtenir le pouvoir histaminopexique le plus éleve avec le minimum de protides et nous l utilisons fréquemment dans nos etudes sur l histaminopexie

b) *La sérumalbumine*

La serumalbumine est obtenue apres délipidation du serum par l acetone puis elimination des globulines par barbotage de CO_2 (Adnot 1931) elle est ensuite soumise à une dialyse prolongee et enfin remise en solution dans du liquide de Tyrode elle se montre alors capable de capter l histamine (technique pharmacologique)

2 ROLE DU POTASSIUM ET DU CALCIUM — Le serum sanguin contient un inhibiteur de l histaminopexie cette notion se degageait deja des experiences de dialyse (Parrot Urquia et Mlle Laborde 1952) le sérum ainsi debarrasse des élements diffusibles qu il contient acquiert un pouvoir histaminopexique de plus en plus eleve la valeur de celui-ci se stabilise aux environs de 50 p 100 (technique pharmacologique) (V fig 2) Puis nous avons pu montrer en effet que le dialysat de sérum exerce une activite inhibitrice sur l histaminopexie enfin cette inhibition a pu etre attribuée au potassium (Parrot Mlle Laborde et Mll Dambrine 1955) les deux

arguments expérimentaux qui conduisent a cette conclusion sont les suivants 1° il suffit d augmenter faiblement la concentration du liquide de Tyrode en chlorure de potassium (215 mg/l au lieu de 210 mg/l) pour faire disparaitre l histaminopexie d un serum normal evaluee dans les condi

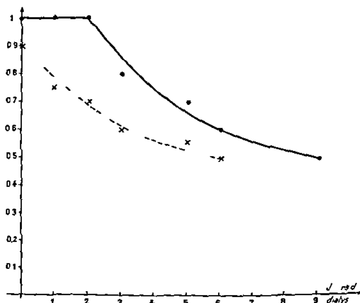


Fig 2 — Activité biologique de l histamine mise en présence de serum humain et ses modifications sous l influence de la dialyse 5 ml de sérum sont mis à dialyser aux environs de 0° dans un sac en collodion qui baigne dans 25 ml d eau distillée additionnée de 9 p 1000 de ClNa Le bain est renouvelé trois fois par jour

En abscisses jour de dialyse au temps o sérum non dialysé
En ordonnées activité biologique de l histamine titrée sur l iléon isole du cobaye La valeur 1 représente l activité totale de la solution de dichlorhydrate d histamine a 10 ⁶
Les lots d expérience contiennent le sérum à la concentration de 1/20 et le dichlorhydrate d histamine à la concentration de 10 ⁶ Sérum d asthmatique trait plein et points Serum normal trait pointillé et croix

tions habituelles de la technique pharmacologique 2° la quantite de potassium contenue dans le dialysat de sérum dosee au photometre à flamme correspond a l activite inhibitrice de ce liquide

Des recherches en cours nous montrent que le calcium s oppose a l action du potassium en effet lorsque l histaminopexie a été inhibée par un léger exces de potassium elle peut etre rétablie par l addition de calcium (recherches inedites avec Mme Mordelet Dambrine)

3 Le plasma total — Seule l activité de la γ globuline histaminopexique peut etre ici envisagée car la sérum albumine ne capte pas l histamine dans le plasma normal le taux de potassium est tel en effet dans ce milieu qu il inhibe totalement l activité histaminopexique de la sérum albumine bien plus lorsque cette fraction est isolée du plasma par la méthode

d'Adnot (1931) elle inhibe au contraire l'histaminopexie d'un sérum normal et cette activité inhibitrice est justifiée par la quantité de potassium présente dans cette fraction.

d) DONNÉES CLINIQUES

Le pouvoir histaminopexique du plasma ou du sérum de l'Homme adulte normal mesuré par la technique pharmacologique est en moyenne de 33,2 ± 8,8 calculé sur 51 individus.

Les recherches poursuivies par P. H. Vignes dans notre laboratoire montrent qu'il existe un léger abaissement de l'histaminopexie plasmatique au cours du travail d'accouchement.

Sur 70 malades divers non allergiques nous avons trouvé la valeur de 28,0 ± 8,9 qui ne diffère pas significativement de la valeur trouvée chez le sujet normal. Le tableau II indique les valeurs trouvées en fonction du diagnostic. Aucun de ces 70 malades n'avait de pouvoir histaminopexique nul.

TABLEAU II

Pouvoir histaminopexique du sérum sanguin chez les malades non allergiques
(Parrot et Mlle Laborde 1953)

DIAGNOSTIC	NOMBRE DE SUJETS	POUVOIR HISTAMINOPEXIQUE MOYEN
Cardiopathies valvulaires sans antécédents rhumatismaux	6	32
Phlébites des membres inférieurs et varices	4	31
Infarctus du myocarde	5	28
Cancers	18	27 ± 9,6
Hypertension	5	26
Tuberculoses sans manifestation allergique importante	5	24
Gastrites (non ulcéreuses)	10	20 ± 8,1
D[illegible]	17	28 ± 8,3

On remarquera dans ce tableau où les valeurs du pouvoir histaminopexique ont été classées par ordre décroissant que les malades atteints de gastrites, même en dehors de tout ulcère gastrique ou duodénal, ont une histaminopexie plasmatique particulièrement abaissée.

II. L'ABSENCE D'HISTAMINOPEXIE PLASMATIQUE CHEZ L'ALLERGIQUE

A. Données cliniques

L'absence d'histaminopexie est une caractéristique sérologique qui coïncide remarquablement avec la notion clinique de terrain allergique au sens large du mot. Sur le millier de malades allergiques que nous avons

aujourd hui etudie avec Mlle Laborde l histaminopexie plasmatique est *nulle dans* 97 p 100 des cas environ Au contraire, sur plus de 200 sujets *non allergiques* soit normaux soit malades nous n avons pas une seule *fois rencontre l* absence d histaminopexie plasmatique il convient cependant comme on le verra plus bas d exclure de ce nombre les malades dont le serum donne des chiffres anormalement eleves au test du thymol

Chez *l allergique* l absence d histaminopexie plasmatique s accompagne constamment d hyperhistaminemie plasmatique et, dans la moitie des cas d un abaissement de la *résistance capillaire*

Deux grandes categories doivent etre distinguées selon que l absence d histaminopexie est permanente ou periodique

a) *L ABSENCE D HISTAMINOPEXIE PLASMATIQUE EST PERMANENTE*

Le plasma reste depourvu de pouvoir histaminopexique que l organisme se trouve ou non exposé aux agressions qui declenchent les crises Il parait tres vraisemblable que l histaminopexie plasmatique etait deja nulle avant toute manifestation clinique D ailleurs nous avons pu saisir le fait dans un cas etudie avec Sclafer il s agissait d un enfant de cinq ans dont l histaminopexie plasmatique était nulle et qui ne présentait aucune manifestation clinique or à six ans il allait etre atteint de crises d asthme Mais il peut arriver aussi comme le montre un cas observe par Mlle Laborde que l histaminopexie plasmatique soit d abord normale puis qu elle diminue progressivement a l âge adulte et qu elle s annule enfin quelque temps avant l apparition des premieres crises de migraines

On retrouve parmi les ascendants d autres personnes dont le plasma presente les *memes* caracteristiques et avec Sclafer nous avons meme pu depister dans quelques cas l existence de transmetteurs sains

Il semble bien qu il s agisse ici d un *genotype*

1 Asthme et rhume des foins — Nous avons etudié avec Mlle Laborde *79 cas d* asthmes typiques (v fig 1) Trois de ces malades seulement ont fourni un serum doue de pouvoir histaminopexique et ce dernier etait tres faible (5 5 10) Chez tous les autres l histaminopexie plasmatique etait constamment nulle meme loin des crises Il en etait de meme dans deux cas typiques de rhume des foins Jeune et coll (1957) notent une histaminopexie nulle 10 fois sur 12 asthmes

2 Urticaire et œdème de Quincke — Sur les 20 cas étudies avec Mlle Laborde (1953) tous avaient une histaminopexie constamment nulle meme loin des crises Il nous parait interessant de noter que dans plusieurs de ces cas il s agissait d urticaire provoquée par le froid la fatigue ou encore par une simple pression exercée sur la peau

Pellerat et coll (1957) sur 6 cas Wodniansky (1957) sur 11 cas trouvent toujours des valeurs faibles ou nulles

3 Migraine — Onze cas de migraines ont éte suivis avec Mlle Laborde 10 fois le pouvoir histaminopexique s est montre nul et cela meme loin des crises 1 fois positif mais tres faible (5)

b) *L HISTAMINOPEXIE NE DISPARAIT QU'A L OCCASION DE LA LÉSION*

Il y a lieu de croire dans ces cas que le pouvoir histaminopexique était normal avant les premieres manifestations cliniques

1 RECTOCOLITE HÉMORRAGIQUE — Avec Charles Debray et Mlle Laborde (recherches inédites sur 29 malades) nous avons constaté que l histaminopexie plasmatique est nulle au moment de la poussée de rectocolite hémorragique mais elle reprend une valeur normale entre les poussées

2 ULCÈRES GASTRIQUES OU DUODÉNAUX — Nulle au cours de la poussée ulcéreuse (88 fois sur 89 mesures) l histaminopexie plasmatique se rapproche de la normale entre les premières poussées mais sans l atteindre et s annule de nouveau quelques jours avant le début clinique de la poussée suivante Plus tard lorsque l ulcère vieillit l histaminopexie reste constamment nulle C est ce que nous avons observé avec Mlle Laborde Ch Debray et Roure (1956) sur 74 malades

Pellerat et coll (1957) étudient 24 malades en poussée 21 fois l histaminopexie est nulle

3 ECZÉMA (V tableau III)

TABLEAU III

Eczema en cours d évolution

RÉFÉRENCES	NOMBRE DES CAS ÉTUDIÉS	HISTAMINOPEXIE NULLE NOMBRE DES CAS
Parrot et Mlle Laborde (1953)	15	14
Parrot Sidi et coll (1957) Sidi Reinberg et coll (1958)	122	107 (nulle ou abaissée)
Jeune et coll (1957)	12	10
Pellerat et coll (1957)	24	21
Wodniansky (1957)	74	62 (nulle ou inf à la normale)
	Totaux 247	214

L histaminopexie plasmatique s élève lorsque les lésions cutanées *régressent*

4 RHUMATISME ARTICULAIRE AIGU — Le pouvoir histaminopexique du plasma s annule au moment de la crise rhumatismale Puis il revient à la normale si aucune lésion cardiaque ne persiste Il reste nul dans le cas contraire même si la lésion paraît cliniquement stabilisée et cela même de nombreuses années après la dernière crise rhumatismale Tels sont les principaux résultats de l étude que nous avons entreprise avec Mlle Laborde (1953) et poursuivie avec Mozziconacci Mlle Danelatos et Mlle Laborde (1957) (voir aussi Danelatos 1955) sur un total de 60 malades (52 enfants et 8 adultes) Jeune et coll (1957) notent que l histaminopexie est nulle 6 fois sur 8 cas de rhumatisme articulaire aigu

5 RHUMATISME CHRONIQUE ET GOUTTE TUBERCULOSE A MANIFESTATIONS ALLERGIQUES — Des etudes systematiques restent a faire pour compléter les premiers resultats observes dans ces cas (Parrot et M^lle Laborde 1953)

6 PURPURA ALLERGIQUE — L histaminopexie plasmatique est nulle ou abaissee au cours des poussees de purpura allergique (recherches inedites avec Jean Bernard Mathe et M^lle Laborde)

B Données chimiques

Le probleme est de savoir en quoi differe le plasma chez l homme allergique et chez l homme normal Ce probleme n est pas entierement resolu En voici les donnees actuelles

a) *LE SÉRUM DE L ALLERGIQUE N EST PAS DÉPOURVU DE MOLÉCULE HISTAMINOPEXIQUE*

Lorsque le serum d un asthmatique est soumis a une dialyse prolongee il devient capable au bout de 3 jours environ de capter l histamine Son pouvoir histaminopexique va ensuite s accroissant pour atteindre la valeur de 50 p 100 vers le 9^e jour En somme il suit a peu pres la meme courbe que le pouvoir histaminopexique d un serum normal soumis a la meme épreuve mais avec un retard d environ 3 jours (voir fig 2) (Parrot Urquia et M^lle Laborde 1952)

b) *L ABSENCE D HISTAMINOPEXIE N EST PAS LE FAIT D UN EXCÈS D INHIBITEUR*

L epreuve precedente parait suggerer que l equipement histaminopexique serait le meme dans les deux plasmas mais que chez l allergique un inhibiteur diffusible se trouverait en exces L experience devait montrer qu il n en est rien

Tout d abord la molecule histaminopexique n a pas ete saturee simplement par l histamine qui se trouve en exces dans le plasma des allergiques Ceci resulte de comparaisons entre le taux d histamine et la valeur de l histaminopexie avant et apres dialyse de 24 heures sur les deux types de serums (Parrot Urquia et M^lle Laborde 1952)

D autre part nous avons pu identifier au potassium la substance diffusible qui limite l histaminopexie du plasma (Parrot M^lle Laborde et M^lle Dambrine 1955 et recherches inédites) or les allergiques ne presentent pas en général d hyperkaliemie c est un fait que nous avons éte en mesure de confirmer avec M^me Mordelet Dambrine (recherches inédites)

c) *LE PLASMA D ALLERGIQUE DIFFÈRE DU PLASMA NORMAL PAR LA NATURE DE SES PROTÉINES*

Replacees dans les memes conditions de milieu salin (liquide de Tyrode) les proteines plasmatiques sont incapables de capter l histamine si elles proviennent d un sujet allergique (recherches inedites avec M^me Mordelet Dambrine) elles en fixent environ 30 p 100 si elles proviennent d un sujet normal La fraction histaminopexique n est donc pas de meme nature dans l un et l autre cas Il y a dysglobulinémie dans le cas de terrain allergique

d) *ESSAI DE SÉPARATION*

Si l on dilue le plasma au 1/15 dans de l eau distillée et qu on l amene a *p*H 5 2, la fraction histaminopexique passe dans le précipité s il s agit d un sujet normal elle reste en solution s il s agit d un allergique (recherches inedites avec Mlle Laborde)

Bien que d autres recherches soient necessaires sur ce sujet il semble probable que la gamma globuline histaminopexique qui est presente chez le sujet normal soit absente chez le sujet allergique

Des essais recemment entrepris avec Mme Mordelet Dambrine et Mlle Laborde nous montrent que les sérums qui donnent une valeur anormalement elevée au test du thymol sont dépourvus de pouvoir histaminopexique On sait que ces valeurs anormales au test du thymol sont attribuees notamment a une modification des gamma globulines Ce cas particulier vient donc montrer encore l importance de la fraction gamma globuline dans le mecanisme de l histaminopexie plasmatique Mais ici contrairement au cas du terrain allergique la dialyse prolongee ne fait apparaitre aucune activite histaminopexique Il s agit donc d une modification differente des gamma globulines

III L HISTAMINOPEXIE PLASMATIQUE ACQUISE

Nous avons pu faire acquerir aux allergiques une histaminopexie plasmatique de valeur normale en leur injectant du serum humain normalement histaminopexique En meme temps les crises particulieres au malade disparaissent Ces modifications cliniques et serologiques paralleles temoignent semble t il d une immunite antihistamine acquise

La resistance du Cobaye a l action de l histamine et ses variations à la suite d une injection de serum humain avaient eté etudiees par Benda et Urquia a partir de 1948 (voir Benda et Urquia 1950) ces auteurs avaient constate que si le sérum provenait d un sujet non asthmatique il pouvait conferer une certaine protection au Cobaye s il provenait au contraire d un asthmatique il ne protegeait aucunement l animal et ces auteurs parlaient de « terrain asthmogene » D autre part ils avaient traite les asthmatiques avec succès par injection de serum humain provenant de sujets non asthmatiques

Mais le problème e t plus vaste L etude du pouvoir histaminopexique nous a permis de constater que l anomalie plasmatique observée chez les asthmatiques n est pas particuliere à ces malades Nous avons montré plus haut comment l absence d histaminopexie plasmatique est un test de terrain allergique au sens le plus vaste de ce terme Il y avait donc lieu d examiner si l inj

cutanés

disparu

dans ce sens mais jusqu ici nous avons obtenu des resultats satisfaisants dans tous les cas ou nous avons tenté le traitement asthmatiques urticariens migraineux eczémateux Nous avons expose ailleurs ces premiers resultats (Parrot et Mlle Laborde 1956) Nous nous bornerons ici a etudier

l histaminopexie plasmatique des malades ainsi traites (Parrot et Mlle Laborde 1953 1954 1956 Parrot Mlle Laborde et Mme Mordelet Dambrine 1958) leur plasma acquiert en effet un certain pouvoir histaminopexique en meme temps l histaminemie plasmatique qui était anormalement elevee se rapproche de la normale, et la resistance vasculaire qui dans la moitie des cas etait abaissee revient a la normale

A Caracteres du pouvoir histaminopexique acquis

a) *ÉVOLUTION CHRONOLOGIQUE*

L evolution chronologique du pouvoir histaminopexique acquis est assez variable (v fig 3) Il apparait habituellement avant l amelioration

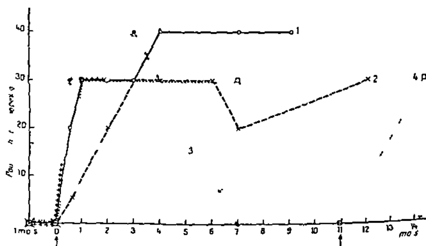


FIG 3 — Pouvoir histaminopexique du serum exprimé en pourcentage de l histamine inactivée (ordonnée) et ses variations en fonction du temps chez 4 malades allergiques 1 – M L 29 ans urticarien 2 – Mme M 45 ans migraineuse 3 – Mme S 29 ans asthmatique 4 – Mlle B 53 ans presentant des poussées d ulcere gastrique Aux fleches injection sous cutanée de sérum humain normal la première concerne les 4 sujets la seconde Mlle B

clinique c est lorsqu il atteint la valeur de 20 environ que celle ci se manifeste avec netteté lorsqu il acquiert la valeur de 30 environ au bout de trois semaines a trois mois les crises ont généralement a peu pres completement disparu

L histaminopexie se maintient à des valeurs à peu pres normales pendant *quelques mois ou quelques annees (plus de trois ans chez certains de nos* malades) Enfin elle decroit et les crises reparaissent

Si malgre le traitement l histaminopexie du malade reste nulle aucune amelioration clinique ne se manifeste (2 cas sur 27 malades)

b) *QUANTITÉ D HISTAMINE FIXÉE*

Il se trouve que dans les conditions standardisees pour son evaluation pharmacologique le pouvoir histaminopexique du plasma fournit à peu pres les memes valeurs (environ 30 p 100) qu il soit inne ou acquis Mais l étude

systematique du phenomene grâce a l ultrafiltration nous revele une importante difference quantitative (recherches en cours avec Mlle Laborde et Mme Mordelet Dambrine) l histaminopexie acquise se trouve saturee par des quantites d histamine beaucoup plus faibles que l histaminopexie innée (v tableau IV)

TABLEAU IV

Pourcentage d histamine non ultrafiltrable en fonction de la surcharge du plasma humain en histamine (chaque chiffre correspond à une valeur individuelle)

SURCHARGE D HISTAMINE (d hlo hyd ate) en μ ml d plasma		30	0
Pourcentage d histamine non ultra filtrable par rapport à l histamine l bre	Histaminopexie innée	15 20 45	35
	Histaminopexie acquise	0 0 0	7 30 35

Plus exactement le pourcentage se trouve inférieur au seuil différentiel de la méthode de dosage qui est de l ord e de 5 p 100

c) *INHIBITION PAR UN COMPÉTITEUR*

L addition d une azoproteine d histamine (**) au plasma permet de differencier les deux mecanismes de l histaminopexie plasmatique meme a une tres faible concentration (10^{-7}) ce corps fait disparaitre le pouvoir histaminopexique acquis Or à une concentration 25 000 fois plus elevee il ne modifie pas le pouvoir histaminopexique inne Semblables resultats peuvent etre obtenus avec l histamine azo paranitraniline

d) *ACTION DU CHAUFFAGE*

Lorsqu on chauffe le serum sanguin pendant 20 minutes a 56 °C le pouvoir histaminopexique persiste si le serum provient d un sujet non allergique il disparait s il provient d un malade allergique traite par le serum humain normal L etude systematique du chauffage pendant vingt minutes a diverses temperatures montre que la temperature de 56 °C est bien la plus basse qui pour cette duree permet de faire completement disparaitre le

(*) Obtenue à part r de protéines sé ques déspéc fiées de Cheval l s agit du Lert gon qui a été gracieus ment fourn pa Park Davis and C

pouvoir histaminopexique acquis (voir fig 4) On peut le restituer apres chauffage par l addition de serum frais de Cobaye pour cette épreuve il

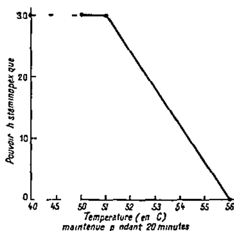


FIG 4 — Pouvoir histaminopexique acquis du sérum Effet du chauffage (Parrot Mlle Laborde et Mme Mordelet Dambrine 1958)

fallait que le serum ajoute fut lui meme depourvu de pouvoir histamino pexique le serum de Cobaye scorbutique s est montré propre à cet usage

B Le pouvoir histaminopexique acquis comme test d immunite antihistamine

Une hypothese permet de rattacher l histaminopexie acquise a l histami nopexie innee le sérum humain normalement histaminopexique fournirait a l organism allergique un antigène complexe dont ce dernier est dépourvu il s agit de l ensemble constitue par la globuline histaminopexique et l his tamine cette dernière substance peut jouer le role d haptène et déterminer la specificite antigenique Selon cette conception le pouvoir histaminopexi que resulte d une reaction entre l anticorps et l haptène le complément parait indispensable a cette réaction comme le montre l épreuve du chauf fage quant a l action de l azoprotéine d histamine elle se comprend par faitement il s agirait d une saturation de l anticorps par un antigène

Cette conception conduisait a une expérience il devait etre possible en effet d obtenir les memes résultats therapeutiques en utilisant non le serum humain normal dans sa totalité mais seulement deux de ses elements la globuline histaminopexique et l histamine

A defaut de la globuline histaminopexique que nous ne possedons pas à l etat pur nous avons employe des gamma globulines humaines nous les avons utilisees à la concentration de 6 mg par ml qui est voisine de la concentration plasmatique

Des experiences faites sur le Cobaye avec Urquia et Mlle Laborde nous montrerent alors que l on pouvait protéger cet animal contre l histamine

au moins aussi bien qu'avec le sérum humain total en lui injectant par voie sous cutanée 2 ml d'une solution contenant à la fois gamma globulines et histamine L'injection de l'une ou de l'autre de ces deux substances isolément et à la même concentration est sans effet Une série de solutions avait été préparée les deux solutions qui se montrerent les plus efficaces contenaient 0 0625 et 0 0750 µg de dichlorhydrate d'histamine par ml

Nous avons alors traité divers allergiques par l'injection sous cutanée de 2 ml d'une solution contenant les gamma globulines humaines a la concentration de 6 mg/ml et le dichlorhydrate d'histamine a la concentration de 0 075 µg/ml Cette étude a porté sur 43 malades (20 asthmatiques 11 migraineux 6 urticariens 6 eczemateux) Dans 38 cas nous avons observé une nette amelioration clinique

Sur 21 des 43 malades nous avons pu etudier le serum et nous avons vu apparaitre un pouvoir histaminopexique de type acquis chez 18 d'entre eux c'est a dire chez tous ceux qui se sont trouves amelio res Par contre le pouvoir histaminopexique du serum est resté nul chez les 3 autres malades or leur etat n'avait pas ete modifié par le traitement

Cet ensemble de resultats semble montrer que le pouvoir histaminopexique acquis temoigne bien d'une immunite antihistamine Ce n'est pas la premiere fois qu'une telle immunite est obtenue Deja divers auteurs (voir Fell et coll 1943 Went et Kesztyus 1951) ont pu la realiser chez l'animal et chez l'Homme Mais ces auteurs utilisaient des azoproteines d'histamine formées avec des proteines etrangères a l'espece humaine

RÉSUMÉ

1 Le plasma humain normal contient une gamma globuline capable de fixer une fraction de l'histamine ajoutée *in vitro*

2 La gamma globuline histaminopexique du plasma normal n'existe pas chez les sujets allergiques Cette anomalie serique caractérise le terrain allergique Elle parait dans certains cas se transmettre hereditairement Il s'agit alors vraisemblablement d'un genotype

3 D'autres recherches sont necessaires pour savoir comment se comporte dans l'organisme la gamma globuline histaminopexique On retiendra cependant que lorsque l'histaminopexie plasmatique est absente l'organisme est plus sensible a l'histamine par exemple dans le cas du Rat surrenalectomisé du Cobaye scorbutique et de l'Homme allergique

4 L'emploi de l'histamine a pu fournir un test commode pour deceler la presence ou l'absence d'une gamma globuline particuliere Mais cette derniere peut capter d'autres substances la recherche de celles ci est encore a ses débuts Il est possible que les diverses manifestations de l'allergie soient attribuables à diverses substances normalement retenues par cette meme globuline

5 L'histaminopexie acquise par le plasma chez l'allergique a la suite d'une injection de serum humain normal temoigne d'une immunite antihistamine

SUMMARY

1 The human normal blood plasma contains a gammaglobulin capable of fixing part of the histamine added *in vitro*

2 The histaminopexic gammaglobulin which is present in normal [illegible] Th[illegible] abnormality carac

3 A new research is necessary to know how the histaminopexic gamma globulin behaves in the circulating blood It should be kept in mind however that when the plasma histaminopexy is absent the organism is more sensitive to histamine as for instance in the case of the adrenalecto mized rat and scorbutic guinea pig

4 The use of histamine has provided a convenient test for the detection of the presence or absence of this particular gammaglobulin but however this globulin is able to fix also other substances and this study is now still at its initial stage It is possible that the various allergic symptoms can be attributed to various substances which are normally kept bu the same globulin

5 Acquired histaminopexy of the plasma in allergic patient following the inflexion of normal human serum proves a certain degree of antihista minic immunity

ZUSAMMENFASSUNG

Das menschliche Blutplasma enthalt ein Gammaglobulin welches einen Teil des « in vitro » hinzugefugten Histamins binden kann

Dieses im normalen Plasma existiernde histaminbindende Gammaglo bulin kommt im Plasma der Allergiker nicht vor Diese Anomalie charakte risiert das allergische « Terrain » Sie scheint in gewissen Fallen vererbbar zu sein Es handelt sich dementsprachend um einen Genotypus

Weitere Forschungen zum Verhalten dieses histaminbindenden Gamma globulins im zirkulierenden Blut sind notwendig Es ist hervozuheben dass bei Abwesenheit der Plasmahistaminopexis der Organismus viel empfund licher auf Histamin reagiert Z B im Falle der adrenalektomierten Ra te oder beim skorbutischen Meerschweinchen

Die Anwendung von Histamin ist also ein einfacher Test zum Nachweis von vorhandendem oder abweisendem specifischen Gammaglobulin Dieses jedoch kann ebenfalls andere Substanzen binden deren Aufklarung allerdings noch ganz in den Anfangen steckt Es ist moglich dass die aller gischen Manifestationen durch diese verschiedenen Substanzen norma lerweise durch dasselee Globulin genbundem hervorgerufen werden

Acquerierte Plasma Histaminopexis beim Allergiker, als Folge einer Injektion von normalen menschlichen Serum weisst eine antihi tamine Immunitat nach

RESUMEN

1 El plasma humano contiene una gama globulina capaz de fijar una cierta cantidad de histamina « in vitro »

2 La gama globulina histaminopexica del plasma normal no existe en los sujetos alergicos Esta anomalía serica caracteriza el terreno alergico En algunos casos parece trasmitirse hereditariamente Se trataría por lo tanto de un genotipo

3 No se conoce exactamente el comportamiento de la gama globulina histaminopexica en la sangre circulante Se observa no obstante que cuando la histaminopexia no existe el organismo es más sensible a la histamina como por ejemplo en el caso de la rata suprarrenalectomizada o el cobayo escorbutico

4 El empleo de la histamina constituye un test cómodo para investigar la presencia o ausencia de una gama globulina particular Esta globulina sin embargo puede captar seguramente otras sustancias cuya investigacion está en sus comienzos Es posible que las diferentes manifestaciones alergicas se deban a diversas sustancias normalmente retenidas por la misma globulina

5 El hecho que el plasma del sujeto alergico sea capaz de adquirir poder histaminopexico luego de una inyección de suero normal indica que existe una inmunidad antihistamínica

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THE RELATION OF HISTAMINE LIBERATION TO ANAPHYLAXIS

by

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Possibly the most intriguing problem in allergy is still that of how a piece of sensitized smooth muscle comes to contract promptly and vigorously when exposed to the proper antigen and I should like to discuss some of the recent work on *histamine release in the light of this problem* For a description of the phenomenon it still seems best to return to Dale s 1913 paper and it is interesting to examine how far our recent knowledge goes to answer the questions then raised

At the time a special interest was directed to the possibility that the union of antigen and antibody gave rise to a proteolysis whose products brought about the physiological responses of anaphylaxis

This paper backed up the later one with Kellaway made it impossible to suppose that the contraction of the smooth muscle depended on proteolytic activity generated in constituents of the blood since blood appeared totally unnecessary for the response In addition the time *relationships* of the contractile response to antigen viz its short latency its rapid development and early maximum comparable with those seen with β iminazole *ethylamine led him to doubt that any local proteolytic events should be* concerned Such a doubt confronts of course any other time consuming enzymatic process Dale expressed his own preference at the time for the conception that the union of antigen with cellular fixed antibody created a disturbance of the colloid equilibrium of the limiting membrane of the smooth muscle

The subsequent discovery of the analogies between the response of various tissues to histamine and in anaphylaxis and of the fact that histamine is released in many of the situations of antigen antibody union gave a new direction to research diverting it somewhat away from the *study of the contractile response itself and towards an analysis of histamine* its release and its actions so that pharmacological evidence of histamine release rather than the responses of smooth muscle or blood vessels came to be used extensively and profitably in the analysis of the antigen antibody effects But as it became clear that tissues artificially desensitized or

already insensitive to histamine could still yield an anaphylactic response the correlation of histamine release with effective antigen antibody union began to fail Our position is indeed not that we have advanced far towards solving Dale's original problem but that we have acquired more problems bearing perhaps different solutions More recently a further development has taken place the discovery that histamine is largely but not only located in mast cells and that the process of histamine release is associated with the degranulation or disruption of these cells Fascinating as these developments are they carry us perhaps another step away from the anaphylactic contraction itself as we study not the contraction nor the hormones which may cause it but the morphological changes associated in an obscure way with the mobilization of hormones possibly involved

We must still ask therefore whether the three processes seen in anaphylaxis — mast cell change local hormone release muscle contraction — constitute a causal chain or no? Are they as it were in series or in parallel or both? And further do studies with chemical releasing agents throw any light on the problem?

HISTAMINE LIBERATORS AND PROTEOLYSIS IN ANAPHYLAXIS

It seems tolerably clear that despite some remarkable analogies there are major differences between the action of liberators and of anaphylactic antigen Some are only to be expected thus the incidence of effect of a liberator will depend simply on its distribution and that of releasable histamine but in anaphylaxis the distribution of bound antibody will also be important But two special points are of interest If one considers the time course of histamine release *in vivo* or in a perfused organ it is remarkably rapid with liberators but with antigen a little sluggish in comparison With a liberator the depressor response in a cat occurs almost exactly at the time when blood returns rich in histamine from the tissues and reaches the systemic blood vessels again the peak histamine concentration in the blood is within a minute or two of injection in a perfused muscle or skin flap vasoconstriction from the released histamine occurs promptly But with antigen the latency is longer the histamine release in skin is long drawn out and reaches a slow maximum One cannot attribute such differences simply to the time taken for protein to reach the tissues if one recalls the rapid effect of antigen applied to the serosal surface of say a piece of sensitized uterus or gut If then one wishes to exploit the analogies between histamine liberators and anaphylaxis by ... it could only ... rator is formed ... e The same conclusion flows from the second major difference the fact shown by Mongar and Schild and fully discussed by them that anaphylactic histamine release but not release by 48/80 or octylamine is blocked by enzyme inhibitors and that with isolated intracellular histamine rich particles

antigen is now ineffective in release but chemicals still function

One must pause to ask however whether it is worth considering the possibility of liberator formation in anaphylaxis Although I don t think any very plausible hypothesis can yet be framed there are some features which make one reluctant to abandon the possibility altogether In the first place there is the high activity of many liberators Compound 48/80 the substituted butylamine L 1935 the purified material from Ascaris obtained by Uvnas and his colleagues are able to mobilize the histamine *in vivo* and in perfused tissues and to degranulate mast cells in such low concentrations as to rank among the more active compounds at a pharmacologist s disposal It is almost a metaphysical point but there is abundant precedent to back one s suspicion that any synthetic compound of a high potency is a pointer or more than a pointer to the chemistry of the body itself The acetyl ester of choline and a certain phenylethylamine derivative are notable examples We can say too that action of this type is not just a chemist s artefact it is shown by products of natural origin such as certain polypeptide antibiotics by peptones and even by the basic amino acids themselves This would point to products of proteolysis as the most plausible source of anaphylactic liberator The liberators are in addition for the vast majority of cases basic compounds We have therefore to consider a proteolysis allowing the appearance of basic polypeptides This indeed is not improbable Of intracellular proteases the cathepsin II of Bergman is said to resemble trypsin in its reactions and trypsin specifically attacks bonds adjacent to lysine or arginine residues so that a result of trypsin digestion is the appearance of terminal lysine or arginine residues It is interesting that trypsin is the proteolytic enzyme *par excellence* with which anaphylactoid shock is produced—fact harnessed by Rocha e Silva to an earlier proteolytic theory evolved before we knew much about histamine binding that the histamine could be cleaved enzymatically from a peptide linkage We can suggest then that in the anaphylactic process intracellular cathepsin II may be activated by antigen antibody union to from basic polypeptides

But there are some unattractive features to such a view First is that there is so far as I know no direct evidence for any such process I have tested it by incubating sensitised guinea pig tissues with antigen in a small volume of fluid in the presence of mesenteric mast cells from an unsensitised animal (rat or guinea pig) but could demonstrate no enhanced degranulation Proteolytic events in blood indeed have been demonstrated in allergic responses but they can hardly account convincingly for anaphylactic responses in blood free tissues One may comment however that *a proteolysis of the type postulated might be rather hard to detect* It is not necessary that the products are formed in large amounts if they act in close relation to the effector organ further they could be broken down by the enzyme which forms them—as are the kinins and finally the tests for their presence do not at present have the remarkable sensitivity that is available for assaying say a natural transmitter A second unattractive feature of the theory is its fundamental vagueness The general phrase « products of proteolysis can cover a multitude of sins One could use it to accommodate almost any new fact One might suppose the products to act locally as well as to diffuse to adjacent mast cells so

that the theory is indifferent to the location of releasable histamine One could multiply products to exert actions other than histamine release so that our knowledge that slow reacting substances are released of a poly peptide nature is explicable One could postulate varying rates of formation or destruction to conform with diverse time relationships Clearly one could explain anything Not until proteolysis has been shown and a relevant pharmacological action by its products demonstrated can we really support such a theory Yet in its absence we are left with the problem of what significance to attach to the striking property of histamine liberation displayed specifically by so many organic bases

HISTAMINE LIBERATORS AND LECITHINASE

A stimulating new approach to problems of histamine release has been made recently by Uvnas and his colleagues Their observation that a polysaccharide fraction isolated from hip seeds could prevent histamine release by 48/80 and other liberators from the cat paw and prevent disruption of rat mesentery mast cells led them to suspect that some enzyme process was involved in the liberation process since high molecular weight polyanions can inhibit reversibly a number of enzymes perhaps by blocking free amino groups on the enzyme molecule In a search for enzymes able to degranulate mast cells they found out of about 30 tested only one lecithinase A which was significantly active This was still effective on mast cells which by heating to 45 50°C has been made refractory to 48/80 They suggest that there is on the surface of the mast cell a lytic enzyme that this is normally inactive since the active group is blocked by an inhibitor and that when the inhibitor is removed by conjunction with 48/80 or some other suitable basic compound the enzyme becomes actives and attacks the cell membrane They were able further to render mast cells resistant to liberator action by treatment (in the presence of the liberator) with 1 3 diphosphoimidazole which inactivates enzymes with essential amino groups such as lecithinase A and they could restore sensitivity by dephosphorylation with phosphoamidase

There are a few obscure points in this work Lecithinase for instance is inactive on the perfused cat s paw The action of 48/80 on mast cells was found to be blocked by temperatures between 40°C and 50°C whereas lecithinase is still active at 60°C Lysolecithin itself was rather inactive requiring about 500 μg/ml to have on mast cells the effect produced by Compound 48/80 at 1 μg/ml But this new theory has the attractive features that it accounts for the action of basic liberators that it establishes a new link with the old work on lecithin and lysolecithin and that it could account for the appearance of non polypeptide muscle stimulants such as that described by Brocklehurst It is interesting too in exploiting the idea that activation may be achieved by removal of an *inhibitor* a notion also used by Garcia Arocha Ashwin & Grossberg in the suggestion that liberators combine with heparin so releasing a proteolytic enzyme previously inhibited by heparin Another hopeful feature is that an explanation might be forthcoming for the extraordinary histamine release by large arteries so dependent on species (dextran and egg albumen in rat

polyvidone and Tween 20 in the dog horse serum in cat) whose characteristics Halpern especially has elucidated

It was for a while possible to attribute some of this activity to an action on elements in the blood corresponding to rouleau formation with an aggregation of platelet and leucocytes generally or locally leading to histamine and 5HT release But Halpern s observation that dextran is effective on rat skin *in vitro* renders this view untenable If however an enzymic process mediates the response space at least exists for species variations to operate

The relation of this work to anaphylaxis is not yet clear But it allows us to include lecithinase to intracellular proteases among the enzymes which may play a role

THE ANAPHYLACTIC CONTRACTIONS OF GUINEA PIG ILEUM

How do these phenomena relate to anaphylaxis? I would like to start by outlining simply some of the events seen in the anaphylactic response of guinea pig ileum Suppose one places two strips of guinea pig ileum in the same bath one sensitized to egg albumen the other not sensitized but serving as a test for active substances released If one then adds a large dose of the antigen (say 1 mg when an adjacent piece of gut has been shown to react well to 1 μg) two phenomena impress themselves The first is the irreducible latency of response by the sensitized strip to antigen — of the order of 12 seconds — whereas an equiactive or less active dose of histamine acts within 1 2 seconds The second is the extraordinary persistence of the spasm of the sensitized strip Soon after its development the unsensitized strip begins to contract But if the bath is now washed out the latter relaxes completely and the sensitized strip is hardly changed With further lapse of time of a few minutes a little more activity accumulates in the bath readily washed out again Soon a state is reached in which the sensitized strip is in a condition of maintained spasm yet there is no sign at all of diffusible active principles escaping from it and this condition can persist for a period of an hour or more If in a similar experiment mepyramine to a concentration of 10^{-7} is added to the bath the sensitized strip now undergoes a somewhat slower contraction (though of little changed latency) but one which carries it to almost as intense and prolonged a spasm as normal yet the test strip shows no activity at all

Such an experiment recapitulates of course some of the classical experiments on anaphylaxis by Feldberg and Schild and their colleagues chiefly on lung and uterus But it seems too to make it hard to believe that the formation of diffusible muscle stimulants account for all the phenomena of the anaphylactic contraction There appears to be no major barrier to diffusion in the muscle spaces for we know that histamine added to the bath can least the outer muscle fibres within a second or two and antigen can be only a little less rapid Further a significant proportion of the histamine released in the anaphylactic reaction can escape into the bath some ten to twenty seconds after the contraction starts There may be of course a very intense local concentration of local hormones at the start of the reaction but there emerges no reason why such hormones should

not diffuse away quite soon and allow the gut to relax as it does after a massive dose of histamine or other stimulant It is true that the relaxation after slow reacting substances is slower than with like histamine or acetyl choline the recovery of the gut from their action or indeed from any other stimulant I know is far faster than the relaxation of the anaphylactic spasm of the ileum Again one might postulate a continuing localised release but this would surely cause activity to appear in the bath fluid Finally one might suggest that the active substances are released and act within the smooth muscle cell and do not escape from it but this is not an attractive idea now that we know from Castillo and Katz s work for instance that acetylcholine acts only on the outside of a motor endplate and is devoid of action given intracellularly The *persistence* of the spasm then in the absence of detectable activity in the surrounding fluid presents a serious difficulty for any theory which attributes the spasm entirely to diffusible stimulants whether histamine or other substances The histamine theory could escape from some of its other difficulties, such as the ineffectiveness of antihistamines by the entirely plausible idea of intense local concentrations but this is hardly possible when diffusional equilibrium has been developing for an hour or more

Such experiments make one return to Dale s conception that the anaphylactic reaction leads to a disturbance of the conditions of colloidal solution in the smooth muscle fibre meaning by that perhaps some process which activates the contractile substance without activating specific chemical receptors Mongar & Schild s work make it probable that some process resembling the enzymic is involved the distinct latency in the anaphylactic response of the ileum despite the great rapidity of the contraction when it appears conforms well with such an idea No great allowance of time is needed here if cholinesterase can remove acetylcholine physiologically in a time of milliseconds then even enzymes with rates or conditions of action a thousand times slower could be considered But Mongar & Schild s work does not necessarily imply as yet the formation of diffusible active principles and an analogy (*mutatis mutandis*) between anaphylaxis and say haemolysin action seems open

If however a relatively biophysical explanation is adopted for the non histamine part of the anaphylactic contraction one must consider whether the breakdown of mastcells and so perhaps the histamine release itself is not also initiated by a similar disturbance of the mastcell membrane We are in short still in a position not far from that of 45 years ago confronted with enzymatic hormonal and biophysical theories or with combinations of them and we still find it hard to choose between them This is perhaps a matter of some practical importance for the problem of seeking an antagonist to an enzyme or to a diffusible stimulant of muscle carries us into the familiar (though in allergy still not very successful) territory of drug antagonism but to modify an activation of smooth muscle which may be brought about by some more direct process is a problem for which we have little guidance save that obtained in the study of the anaphylactic contraction itself

ON THE ROLE OF THE CARRIER IN ANTIGENS

by

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According to the generally accepted theories immunological responses to native full antigens as well as to the artificial complex antigens depend upon the determinant groups in full antigens or the haptenic groups in complex antigens the non determinant remainder of the full antigen molecule or the carrier moiety of a complex antigen are considered to play only the secondary role of an amplifier or support for the specific determinant groups

Formulated in this way—as is generally done—this rule concerns the different types of sensitization indiscriminately But since all results from which this thesis has been deduced have been obtained from experiments in which humoral precipitating or complement fixing antibodies served as a criterion for successful sensitization the validity of this theory should be restricted to atopic sensitization for only here do humoral antibodies determine the specificity and the character of the allergy

Indeed we have no proof that the theory of the carriers unimportance is likewise valid in the elaboration of non humoral sessile antibodies of the delayed type of sensitization

In our opinion it is not correct to make the general statement that the non determinant part of a full antigen and the carrier moiety are unimportant in the process of sensitization The purpose of the following discussions is to rehabilitate the immunological standing of the carriers and of the *allegedly inert part of complete antigens*

Most antigens complete natural antigens as well as numerous chemicals of low molecular weight produce in man and under propitious circumstances in experimental animals various types of sensitizations and different types of antibodies all specifically directed against the sensitizing agent They may cause atopic sensitizations with humoral antibodies in certain individuals contact dermatitis or atopic dermatitis with sessile antibodies in others So far the reasons for this variability of sensitizations have remained obscure Most allergists believe that predisposing factors of the host determine the site of reactivity (weakness of certain organs) and conse

quently the type of antibodies. Others conversely, speak of intrinsic properties of the antigen which determine the type of antibody and thus the site of the sensitization ("atopens", "contactants").

In most discussions on hypersensitivity, we forget that we deal with two separate although interconnected aspects. There is first the specificity of the allergic reaction: the production and reactivity of specific antibodies. The second equally important problem is the form of the specific antibody and the site of the antibody reaction. We do not know which part comes first: the body's choice of the type of antibody or the antibodies' choice of the site of the reaction.

The specificity of the immune reaction is solely concerned with the spectrum of the hypersensitiveness and not with the type of antibody involved: humoral as well as sessile antibodies may possess the same specificity. The second problem, that of the different forms of immune reactions (*evanescent, delayed, neurodermatitic type*) and the different sites of the specific sensitization (smooth muscles, lymph system, collagen ground substance, etc.) is primarily concerned with the chemical or physical nature, the type of the antibody involved.

There is no question as to the correctness of the general concept that the specificity and the spectrum of hypersensitiveness depend solely upon the *determinant groups and the hapten moiety of a complex* antigen. Our attempt to rehabilitate the carrier concerns solely the establishment of the type of specific sensitization and the choice of the reactive site. We believe that the carrier is intimately concerned with this part of the immune reaction; it is even likely that the choice of the type of antibody and the choice of the reactive site are the exclusive domain of the carrier. Thus in my opinion, *far from being inert, the carrier determines the type of antibody formed—humoral, sessile or neurodermatitic, and consequently the site of the allergic reactivity.*

The carriers with which a hapten combines to become a full antigen are usually proteins. At least most of our experience has been with protein carriers. In all the experimental work, one type of protein, namely serum protein or other soluble albumins and globulins or mixtures, has been used almost exclusively. But under normal conditions the organism offers a large choice of different proteins to the haptens, from which they may select the carrier.

Animal organisms contain various types of proteins, such as soluble globular proteins like albumin or globulin, and less soluble or insoluble fibroid proteins like collagen or keratin and their precursors and relatives. The distribution of these proteins in the organism and their ratio in various organs varies widely. Skin, for instance, is rich in fibroid proteins, internal organs are poor; the skin contains 20 times as much collagen as the internal organs. Conversely, epidermis is much poorer in globular proteins than the internal organs. Therefore under natural conditions of sensitization what kind of protein a hapten becomes attached to is a matter of mere chance and accident. *If, for instance, a chemical such as formaldehyde* comes in contact with the skin, most of it will combine quite naturally with the proteins that are prevalent in the skin—skin proteins such as collagen, keratin and their precursors. *But if formaldehyde fumes are inhaled, the* hapten will choose its carrier almost exclusively from among the proteins of

internal organs among which albumins and globulins prevail whereas collagen is quite rare and keratin absent

Different exposure results also in different types of sensitization Formaldehyde when acting upon the skin mostly from without will cause contact dermatitis almost exclusively whereas formaldehyde entering the body via the lungs or the muscles will result in asthma or some other atopic allergic reactivities We encounter the same dependence of the type of sensitization upon the type of exposure with practically all strong sensitizers of low molecular weight

It seems logical to assume that these two processes namely formation of complete antigens and choice of the reaction sites are interconnected and that certain types of carriers are associated with certain types of sensitizations Indeed our own experiments have suggested that the combination of a hapten with an insoluble fibroid protein carrier leads to a full antigen which produces sensitizations of the delayed type with sessile antibodies whereas a combination of the same hapten with a soluble globular carrier protein leads to a complete antigen which produces atopic sensitizations with humoral antibodies Such a correlation is not only in good agreement with but would even explain perfectly the fact that contact of an appropriate antigen with the skin elicits sessile antibodies in the vast majority of cases and that inhalation of the same antigen will produce the humoral antibodies of the atopic reactivity

We have lately discussed the possibility that the combination of a hapten with a carrier of the ground substance which is rich in the fibroid polysaccharides may be the origin of atopic dermatitis and give rise to a still unknown but apparently non circulating antibody in neurodermatitis which differs from the sessile antibodies of the usual delayed types of reactivity

The concept that the physical properties of the carrier determine the type of antibody and consequently the phenomenology of the allergic process would elevate the carriers to a quite important position within the hierarchy of immunity However we cannot ignore any serious objections to such a concept Indeed certain observations apparently contradict my thesis that only fibroid antigens produce sessile antibodies and only globular antigens produce humoral antibodies

It is generally recognized that soluble globular proteins for instance of the serum in foods pollens etc are associated in most instances with sensitizations of the immediate type and consequently with circulating antibodies Nevertheless the same globular proteins are capable of producing sensitizations of the delayed type such as contact dermatitis and in particular neurodermatitis Furthermore sensitizations characterized by delayed reactions are the regular consequence of sensitizations with soluble globular proteins from microorganisms and positive patch tests scratch tests or intradermal tests indicate the presence of sessile antibodies during numerous infectious processes Various authors have been successful in passively transferring these delayed reactivities with cellular material from the host and soluble proteins from the microorganisms

Are these facts compatible with our views enunciated above? Soluble full antigens or soluble complex antigens are immunologically stable provided the determinant groups are not altered So long as a metabolic attack changes only the inert carrier part and so long as the molecular size

does not descend below a certain minimum during a catabolic process, the instrinsic sensitizing power of these soluble antigens remains unchanged and they will be able to produce specific sensitizations

But it is quite conceivable that any chemical or physical alteration of the carrier moiety in complex antigens or of the inert part of a full antigen will influence the type of sensitization and the form of resultant specific antibody

How can soluble globular proteins be changed to such an extent that although they retain their specificity they produce sessile antibodies instead of humoral antibodies as usual? According to the theory proposed here they should lose their globular character assume a rigid form and become fibroid

The first thought is of course denaturation but such a process will also affect the availability of the determinant groups and will lead to a loss of specificity But it is known that soluble proteinic antigens are absorbed to collagen In this way the protein, originally soluble assumes a new configuration and becomes part of a rigid fibroid system This is certainly an interesting reaction, and it would be well worth studying whether such an adsorption of egg protein for instance upon collagen and other fibroid *material of the ground substance will modify its immunological* characteristics to such an extent that it will produce a non atopic dermatitis in which patch tests with egg white are positive

We have studied experimentally the influence of collagen upon the tuberculin reaction which is the prototype of a delayed reaction to a globular protein Old tuberculin as a hapten upon intraperitoneal injection into guinea pigs produces at best only a very few and very weak sensitizations, which are mostly explained by the presence of some bacteria However when tuberculin is injected together with paraffin oil or other so called adjuvants the number and intensity of the sensitizations is sharply increased The same increase occurs when tuberculin is injected after incubation with collagen This result agrees with the theory that adsorption of a globular protein to a fibroid protein conveys to the former the faculty of producing an allergic reactivity of the delayed type It is tempting to explain by the same mechanism the adjuvant action of paraffin oil or Freund s adjuvant in the production of delayed reactions to simple chemicals After injection on unusual sites both produce collagen in the vicinity of the adjuvant deposits It is indeed known that foreign body granulomas and mycobacterial tubercles form large amounts of collagen at an early stage

Today s discussions on the role of carriers have been restricted to the field of sensitizations But the problem of carriers is a much more general one and it certainly is of equal importance in the field of immune protection The role of the carrier in the development of cellular immunity as opposed to humoral immunity is the counterpart of its role in hypersensitivity But time does not permit a consideration of these and many other aspects of the hapten carrier relationship

I have avoided discussing many very important but well known facts on carriers which we can easily read in journals and reviews all I have wanted to present here are a few of the many interesting and unsolved problems that may constitute the bases of new insight in the still mysterious field of hypersensitivity

SUMMARY

A full antigen consists of two parts the determinant group and the non determinant carrier Most allergists believe that the carrier s role merely provides the necessary molecular weight These determinant groups or in the case of complex antigens the haptens or portions of them are responsible for the specificity of the antibody and therewith of the specificity of the allergic reaction whereas in our opinion the carrier is responsible for the type of specific antibody (humoral or sessile) and consequently the type of allergy produced The following theory is discussed Combination of a determinant group with a soluble globular protein carrier will serve as a template for a soluble and therefore humoral antibody combination with an insoluble carrier composed of fibroid protein will produce insoluble sessile antibodies which are responsible for delayed type reactivities Also discussed is the question whether other carriers besides those consisting exclusively of proteins may be responsible for the emergence of other types of allergy such as for instance atopic dermatitis

RÉSUMÉ

Un antigène complet est composé de deux parties le groupe déterminant et le vecteur non déterminant La plupart des allergologistes pensent que le role du vecteur se borne a fournir le poids moléculaire necessaire

Ces groupes determinants ou dans le cas d antigènes complexes les haptenes ou des parties d haptenes sont responsables de la spécificite de l anticorps et de ce fait de celle de la réaction allergique Selon notre opinion c est le vecteur qui determine le type d anticorps specifiques (humoraux ou fixés) et par conséquent celui de l allergie produite

La theorie suivante est discutee la combinaison d un groupe déterminant ayant comme vecteur une protéine globulaire soluble est appelée a servir de support pour former un anticorps soluble et de ce fait humoral sa combinaison avec un vecteur insoluble composé de protéine fibroide produira des anticorps sessiles responsables des réactions du type différé

Une autre question est également discutee d autres vecteurs en dehors de ceux exclusivement composés de protéines peuvent ils etre responsables de l apparition d autres types d allergies comme l eczéma diathésique par exemple?

ZUSAMMENFASSUNG

Ein komplettes Antigen besteht aus 2 Partien die bestimmende Gruppe und die nicht determinierende Tragersubstanz Die meisten Allergologisten nehmen an dass die Rolle der Tragersubstanz auf die Herbeifuhrung des notwendigen Molekulargewichtes beschrankt ist.

Diese bestimmenden Gruppen oder im Falle eines komplexen Antigens die Haptene oder Haptenpartien sind fur die Spezifitat der Antikorper verantwortlich und daher auch fur die der allergischen Reaktion Nach unserer Meinung bestimmt die Tragersubstanz den Typ des spezifischen

Antikörpers (humoraler oder fixierter Antikörper) und daher auch die Form der sich bildenden Allergie.

Folgende Theorie wird diskutiert: die Verbindung einer bestimmenden Gruppe mit einer aus einem löslichen globulären Protein bestehenden Trägersubstanz führt zur Bildung eines löslichen und daher humoralen Antikörpers: ihre Verbindung mit einer aus fibroiden Protein bestehenden unlöslichen Trägersubstanz bedingt fixierte Antikörper, die einen anderen Reaktionstypus verursachen.

Eine andere Frage wird ebenfalls diskutiert: können andere Trägersubstanzen, die nicht exklusiv aus Proteinen bestehen, für das Auftreten anderer Allergieformen verantwortlich sein, wie zum Beispiel des Diathese-Ekzems.

RESUMEN

Un antígeno completo consta de dos partes: el grupo determinante y el transportador (carrier). La mayoría de los alergistas supone que el «carrier» sólo contribuye a alcanzar el peso molecular requerido. En la opinión del autor, por el contrario, el «carrier» determina el tipo de anticuerpo (humoral o sesil) y, por consiguiente, el tipo de reacción alérgica, en tanto que el grupo determinante o, en el caso de antígenos complejos, el haptene son los que confieren la especificidad. El autor expone la siguiente teoría: la combinación de un grupo determinante con un «carrier» soluble constituye un molde para la formación de anticuerpos solubles, es decir humorales; la combinación del grupo determinante con un «carrier» insoluble producirá, en cambio, anticuerpos insolubles, sesiles, responsables de los tipos tardíos de sensibilidad. Se considera también la posibilidad de que puedan actuar como «carriers» sustancias no proteicas, y que en estos casos se obtengan otros tipos de alergia, como por ejemplo la dermatitis atópica.

SYMPOSIUM V

Auto et iso-sensibilisations
Auto and iso-immune reactions
Auto und iso-immunitive Reaktionen
Auto e iso-sensibilizaciones

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INTRODUCTION

by

MAX SAMTER M D

(Allergy Clinics University of Illinois College of Medecine Chicago Illinois)

It is intriguing to realize that a symposium on auto and iso immune reactions would have been impossible at the turn of the century and for years afterwards when immunological thought was dominated by Ehrlich s horror autotoxicus Boyd (1) points out of course that Ehrlich never used the term impossibilitas autotoxica this in retrospect seems fortunate since we have come to accept the fact that man is indeed capable of forming antibodies againts components of his own tissues

Wells (2) outlined in 1929 some ot the possibilities When an animal s proteins are chemically altered they may also behave as foreign proteins and lead to auto antibody formation For example if the serum of an animal is treated with formaldehyde nitrous acid iodin or numerous other substances which combine with the proteins this altered serum may serve as an antigen and give rise to the production of specific antibodies when injected into the body of an animal of the same species from which is was obtained *Probably* some of the tissue proteins of an animal may be foreign to the other tissues of the same animal if they escape into the circulation Thus the protein of the crystalline lens is said to serve as antigen in animals of the same species but if true this iso antibody *formation is not* usually *marked*

Wells apparently used the term auto antigen and iso antigen interchangeably but the multitude of observations which have been reported since his book was written has forced us to define and classify reactions in this area with more rigidity Iso antigens are according to Raffel (3) those antigens which occur in some members of a species only e g the blood group antigens in man or the tissue antigens which prevent skin grafting between individuals of the same species auto antigens tissue antigens which are sufficiently altered to induce immunological mechanism in the species from which they are derived It is true that Burnet s (4) self marker hypothesis with its recognition units awaits further experimental confirmation yet Burnet s efforts have done a great deal to reconcile the horror autotoxicus with the established experience that auto antibodies are formed and that they are responsible for a group of diseases which is surprisingly large

Boyd (1) believes that auto-immunization might be accomplished by intro

ducing into the circulation antigens which are normally confined and that auto immunization more often than not is a man made artificial phenomenon

Wiener (5) outlines three possible pathways for the production of auto antibodies (1) exposure to heterogenetic antigens which are so similar to antigens present in man that the resulting antibody is capable of combining with either (2) the capacity of certain individuals to form antibodies to antigens which are so weak that the rest of the population fails to give an antibody response and (3) the ability of various agents e g bacteria viruses toxins to alter the structure of certain tissue components and render them autoantigenic Wiener s concept is based on his studies of red cells but might apply not only to the formed elements of the blood but to other kinds of tissues yet in many instances it has been impossible to apply knowledge gained in our laboratories to the interpretation of clinical changes which are presumably caused by auto-or iso immune reactions

Masugi (6) provided the experimental foundation for an enlarging field which by now includes every organ and organ system of man Attempts to render homologous tissue antigenic have included autolysis attachment to adjuvants (7) combination with toxin and finally combination with chemicals

Boyd s (1) list of auto immune diseases for instance includes acquired hemolytic anemia chronic leukopenia and physiologic icterus diseases affecting the connective tissue i e collagen diseases certain diseases of the kidney diseases of the eye e g sympathetic ophthalmia diseases affecting the nervous system e g multiple sclerosis (for which the experimental evidence however is less convincing than for demyelinizing encephalomyelitis) and finally some rare diseases of the skin which occur in newborn infants

It seems unlikely that each of these diseases represents t ie clinical expression of an identical immunologic response Sub cl assification might become desirable or necessary One would hardly exp ct to find a unitarian concept which would be able to explain the so called incomplete antibodies of hemolytic anemias, the L F factor in circulating plasma the production of encephalitis by the injection of brain tissue suspended in adjuvant and vascular lesions caused by an antibody to a drug tissue conjugate

The clinical course of auto immune diseases might depend on the extent to which the tissue is involved in the immune mechanism Antigen antibody reactions might cause tissue injury even if tissue acts only as carrier of antibodies and is not as tissue involved in their formation e g anaphylatic reactions induced by heterologous protein it is conceivable that at least some forms of hemolytic anemia might be caused by antigen antibody reactions which happen to take place on the surface of erythrocytes Damage caused by antigen antibody reactions to such carrier tissue is usually reversible antigen antibody reactions on the other hand in which tissue components (e g through the action of haptens) have become part of the antigen tend to be irreversible and at times progressive it

[illegible] mmune diseases

it reflects the intens ty

of allergy It is an area

in which it takes most of our energy to accumulate evidence and sometimes the evidence does not seem to corroborate what we have known or assumed Progress has been spectacular still most of us are bound to feel some of the frustrations which are reflected in a recent editorial in Lancet (8) which reports that it has been impossible to correlate the clinical status of the patient (who suffers from auto immune disease) with his titer of auto immune complement fixing antibodies With the possible exception of auto hæmolytic anæmia none of the natural or experimental diseases attributable to auto immune reactions show any correlation between the amount of circulating antibody and the severity of the disease Possibly the circulating antibody is to be regarded as an epiphenomenon the lesions themselves resulting from cell fixed antibody such as is responsible for tuberculin sensitivity or homograft immunity With a remarkable show of equanimity Lancet prefaces this statement with one sentence which is reassuring and might serve us well during our symposium This is by no means surprising

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LES THROMBO ANTICORPS

par

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Depuis bientot dix ans une littérature abondante est apparue concernant les thrombo anticorps Successivement les auto anticorps responsables de certains purpura thrombopeniques et les iso anticorps permettant de definir des *groupes et des types plaquettaires ont eté postulés*

Et pourtant les sérologistes en sont encore bien souvent a se demander la signification des réactions qu ils observent au laboratoire et les cliniciens a *en attendre des indications diagnostiques et thérapeutiques*

Cependant l immunologie des plaquettes a fait au cours de ces dernieres années d importants progres des techniques plus sures sont maintenant

TABLEAU I

Technique de detection des anticorps anti plaquettaires

In vitro	Lyse
	Opsonisation
	Agglutination à froid
	— à chaud
	Précipitation
	Test de Coombs — direct
	— indirect { consommation antiglobuline / agglutination mixte }
	Fixation du complément
	Inhibition des fonctions plaquettaires de la rétraction du caillot
	— — de la thromboplastinoformation
In vivo	Action chez l homme
	— chez l animal

connues On trouvera dans le tableau I la liste des techniques de detection des anticorps antiplaquettaires dont nous disposons a l heure actuelle

Grâce a ces differentes techniques il peut etre decele des subs

antiplaquettaires que nous classerons d'après les techniques de détection en

— thrombo agglutinines décelées par agglutination aux différentes températures (thrombo agglutinines froides tièdes et chaudes)

— thrombo anticorps incomplets qui ne provoquent pas d'agglutination et sont décelés par la consommation de l'antiglobuline

— thrombo anticorps « allergiques » qui réagissent seulement en présence du médicament

LES THROMBO AGGLUTININES

Rien ne paraît plus paradoxal que de rechercher des substances capables d'agglutiner les plaquettes alors qu'une des fonctions fondamentales des plaquettes est *précisément de s'accoler entre elles*

L'étude des causes d'erreurs de la thrombo agglutination est donc essentielle Nous distinguons la *thrombo agrégation* de la *thrombo-agglutination* (tableau II)

La thrombo agrégation est le premier stade de la métamorphose visqueuse Elle est due vraisemblablement comme l'ont montré *Bounameaux (1)*

TABLEAU II

THROMBO AGRÉGATION Non immunologique	THROMBO AGGLUTINATION immunologique
1er stade de la métamorphose visqueuse due à des traces de { *thrombine* + facteur dialysable Inhibée par SO_4Ba	Réaction antigène anticorps due aux { *iso-anticorps immuns* auto anticorps? Non inhibée par SO_4Ba

et Luscher (2) à des traces de thrombine et à un facteur dialysable Elle est inhibée par absorption sur le sulfate de baryum C'est donc un phénomène non immunologique

Au contraire la thrombo agglutination est un phénomène immunologique provoqué par une réaction antigène anticorps Elle n'est pas inhibée par *absorption sur le sulfate de baryum Elle est due à l'action* d'iso et auto anticorps

Pour éviter la cause d'erreur majeure que constitue la thrombo agrégation, il est nécessaire

— de ne séparer le sérum du caillot qu'après un délai assez long (18 h à 4° C)

— d'inactiver les sérums par chauffage de 30 minutes à 56° C

— de décalcifier les sérums par passage sur résine échangeuse de cations

— d'absorber certains facteurs de la coagulation par passage sur sulfate de baryum

Envisageons successivement les différentes variétés de thrombo agglutinines que l'on peut trouver dans le sérum humain

1° Les anticorps naturels du systeme ABO sont des **iso thrombo agglutinines naturelles** *et sont capables d agglutiner spécifiquement les* plaquettes provenant d individu possédant les antigenes A ou B comme ceci a pu etre démontré par Gurevitch (3) et par nous memes (4) Il restait à savoir si cette agglutination était due a la présence effective des antigenes A et B sur les plaquettes ou si ceux ci étaient seulement des antigenes solubles *plasmatiques absorbés a la surface des plaquettes Apres huit* lavages l agglu tination spécifique est encore présente (tableau III)

TABLEAU III

Présence des antigènes A et B sur les plaquettes lavees

	ANTI A			ANTI B			ANTI A + B		
	PL A	PL B	PL O	PL A	PL B	PL O	PL A	PL B	PL O
1 lavage	++	—	—	—	++	—	++	++	—
3 lavages	++	—	—	—	++	—	++	++	—
5 lavages	++	—	—	—	++	—	++	++	—
8 lavages	++	—	—	—	++	—	++	++	—

2° Beaucoup plus mystérieuses sont les **thrombo agglutinines froides aspécifiques** que l on decèle facilement grace a la méthode d agitation a froid que nous avons decrite avec Malinvaud (5)

Ces substances *ont éte rencontrees dans des* affections *tres diverses* (tableau IV) Elles ne semblent pas jouer un role essentiel dans les purpura quoiqu elles ont éte notees dans 31 % des cas de purpura thrombopéniques aigus et moins fréquemment dans les purpura thrombopeniques chroniques

Elles sont surtout fréquentes et particulierement puissantes dans les cirrhoses hepatiques Elles apparaissent *également fréquentes* (41 % des cas) dans le lupus erythémateux dissémine

Nous voudrions attirer l attention sur un rapport possible entre un anticoagulant et la thrombo agglutinine froide (tableau V) En effet dans six cas ou existait un anticoagulant du type anti thromboplastine une forte thrombo agglutinine *froide était* décelée Par contre dans un seul cas ou l anticoagulant était du type anti thrombine il n y avait pas de thrombo agglutinine *Il est* possible que cette agglutination *soit due* à l action de l anticoagulant sur les facteurs anti hémophiliques A ou B qui se trouvent à la surface des plaquettes dans l atmosphère plaquettaire de Roskam

Nous ignorons si les substances anti plaquettaires decelees à froid sont véritablement des anticorps quoiqu elles soient spécifiquement absorbées sur plaquettes et *qu elles se trouvent* dans les gamma globulines *Il est* possible qu elles représentent un équivalent des agglutinines froides dans la série érythrocytaire

3° *Beaucoup plus intéressantes* semblent etre les **thrombo agglutinines chaudes**

Nous employons pour les *déceler la technique suivante (6)* le *sérum* inactivé décalcifié ... absorbé sur sulfate de baryum et mis au contact

TABLEAU IV

Thrombo-agglutinines froides décelées chez 3 731 malades examinés

	Nombre de cas examinés	Nombre de cas positifs	de positifs
Cirrhoses du foie ou splénomégalies le plus souvent avec thrombopénie modérée	131	46	35 1
Purpura thrombopéniques idiopathiques			
chroniques	66	9	13 6
aigus	18	5	31 1
d évolution inconnue	95	22	22 1
Purpura thrombopéniques symptomatiques			
d une hémopathie maligne	677	19	2 8
d un lupus érythémateux	12	5	41 6
Pancytopénies ou leucopénies diverses	327	17	5 1
Syndromes hémorragiques non thrombopéniques ou de nature inconnue	12	9	12 5
avec anticoagulant circulant	4	4	100
Anémies hémolytiques acquises	186	9	5 3
congénitales	95	6	6 3
Malades ayant reçu du sérum antitétanique	64	10	6 4
Maladies diverses ou inconnues	1 984	19	0 95
Total	3 731	180	

TABLEAU V

Rapport des thrombo-agglutinines froides et des anticoagulants circulants

	Thrombo agglutinine froide
ANTI THROMBOPLASTINES CIRCULANTES	
Cas 1	++ 1/4
Cas 2	++ 1/4
Cas 3	++ 1/4
Cas 4	++ 1/8
ANTI THROMBINE	
Cas 5	—

pendant 30 minutes à 37° avec la suspension des plaquettes lavées La suspension plaquettaire doit être préalablement chauffée de 15 à 18 secondes à 56 °C On agite le mélange sur un agitateur de Kline ce qui favorise considérablement la réaction

Les thrombo agglutinines chaudes présentent les caracteres des anticorps immuns

Elles sont thermostables (30 a 56°) detruites par chauffage 30 a 70° conservees par congélation elles ne sont pas absorbées par le sulfate de baryum ni par le phosphate tricalcique Ce sont des gamma globulines

Elles agissent surtout à 37° dans une gamme de pH allant de 6 9 a 7 6 Elles sont absorbables specifiquement sur plaquettes et sont independantes des anticorps anti érythrocytes que l on peut rencontrer dans un meme sérum Elles ne sont souvent actives que sur certaines variétés de plaquettes

Nous sommes ici en presence d iso anticorps immuns antiplaquettaires En effet tous les malades chez lesquels ces substances ont été decelees avaient reçu de multiples transfusions Il apparait que sur 170 polytransfuses (mot pris dans un sens large a partir de 1 transfusion) 31 développent des leuco anticorps 13 des thrombo anticorps et 9 des erythro anticorps (tableau VI) Mais il se trouve que ce sont le plus souvent les memes malades

TABLEAU VI

Les thrombo agglutinines chaudes (TAC) et eurs rapports avec les leuco-agglutinines (LA) et les erythro-agglutinines (EA)

NOMBRE DE TRANSFUSIONS	NOMBRE DE MALADES	NOMBRE DE TAC	NOMBRE DE LA	NOMBRE DE EA
1 à 10 11 à 20	98 23	2 (0) 1 (0)	7 (5) 3 (2)	5 (2) 1 (1)
p 100 de 1 à 20 transfusions		2 3	8 2	4 9
21 à 30 31 à 40 41 à 100	5 11 16	2 (0) 0 6 (1)	4 (2) 4 (3) 8 (3)	0 1 (0) 1 (1)
p 100 de 21 à 100 transfusions		25	50	6 2
100 transfusions	4	1 (0)	3 (2)	0
Nombreuses transfusions (nombre exact inconnu)	13	1 (0)	2 (1)	1 (1)
Total général	170	13 (1)	31 (18)	9 (5)

Le ch ff ntre parenthèses rep ése tent l nombre d chacun d v riété d gglu t n n qu nt été t u é s *lément* c st-à-d n l ab nce d d ux ut es variétés d gglutin n

qui développent à la fois les leuco et les thrombo anticorps Seulement 2 3 % des malades ayant reçu de 1 à 20 transfusions présentent des thrombo anticorps alors que ces anticorps sont rencontrés chez 25 % des malades ayant reçu de 21 à 100 transfusions Malgré ce chiffre élevé les thrombo anticorps sont deux fois moins frequents que les leuco anticorps

Les thrombo anticorps immuns permettront à l avenir de définir les antigenes plaquettaires et sans doute les groupes plaquettaires Mais la systématisation par groupe n a pas encore été possible

L importance de ces iso anticorps immuns anti plaquettaires en pratique transfusionnelle est peut etre grande Il est probable que la *durée de survie* des plaquettes compatibles *in vitro* est plus prolongée que celle des plaquettes incompatibles Ceci semble être démontré par le fait que dans certains cas la durée de survie diminue au fur et à mesure que les transfusions sont répé tées Il est probable également que certains chocs transfusionnels sont dus à ces anticorps En effet chez une malade qui possédait dans son sérum une iso thrombo agglutinine immune active jusqu au titre de 1/512 sur toutes les variétés de plaquettes testées et chez laquelle chaque transfusion était suivie d un choc très violent nous avons successivement injecté le plasma dépourvu de plaquettes puis le plasma riche en plaquettes un choc violent est apparu immédiatement apres la deuxieme injection

4° Dans deux sérums de malades atteints de syndrome hémorragique dont l un sans thrombopénie nous avons observé une thrombo agglutinine décelable par la meme technique que les thrombo agglutinines chaudes mais dont l optimum thermique se situait à température de laboratoire On pourrait désigner cette variété par le terme de **thrombo agglutinine tiède** Aucun de ces deux malades n avait reçu de transfusions Les substan ces anti plaquettaires ont disparu en meme temps que les troubles La signi fication de ces substances sériques est ignorée

5° Enfin nous arrivons à la cinquième variété d anticorps anti plaquet taires **les anticorps incomplets**

Les « anticorps incomplets » peuvent etre déjà fixés sur les propres pla quettes du malade et sont alors décelés par *le test de Coombs plaquettaire direct* ou bien encore libres dans le sérum et alors détectés par le *test de Coombs plaquettaire indirect* ou ses équivalents en particulier la consom mation de l antiglobuline

a) *Les thrombo anticorps incomplets spécifiques*

Nous désignons sous ce nom les anticorps immuns qui permettent de [illegible] en [illegible] (D) [illegible] l est probable qu il en est de meme pour les autres antigènes du système Rh et pour d autres antigenes d autres systemes (tableau VII)

Les plaquettes des enfants atteints de maladie hémolytique du nouveau né due à l anti D peuvent etre recouvertes d anticorps [Dausset (8)] (ta bleau VIII) mais ce revetement ne provoque qu une thrombopénie modérée et ne s accompagne que rarement d un syndrome hémorragique

b) *Les thrombo anticorps incomplets aspécifiques* Ils sont observés dans les purpura thrombopéniques idiopathiques

1° Le test de Coombs direct plaquettaire a été décrit par Stefanini (9

TABLEAU VII

Présence de l'antigène D (Rh) sur les leucocytes et les plaquettes humaines

	SANG RH POSITIF Consommation		SANG RH NÉGATIF Consommation	
	de l'anti D	de l'antiglobuline	de l'anti D	de l'antiglobuline
Sur leucocytes de leucémie myéloïde chronique	2	3	0	0
Sur plaquettes normales	2 1/2	3	0	0
Sur mélange de plaquettes et de leucocytes normaux	2	3 1/2	0	0

Moyenne du nombre de dilutions géométriques dont le titre de l'anticorps a été abaissé après contact avec les plaquettes et ou les leucocytes.

TABLEAU VIII

Consommation de l'antiglobuline sur les plaquettes d'un enfant nouveau né atteint de maladie hémolytique du nouveau né due à l'anti D

	NOMBRE TOTAL d'éléments dans le test en mill.	1/4	1/8	1/16	1/32	1/64	1/ 250	1/ 560	5	24
Plaquettes										
Malade	8 0	++++	+++	+++	++	—	—	—	—	—
Contrôle	900	++++	+++	+++	++	+	+	(+)	—	—
Sans contact		+++	+++	+++	++	++	++	++	+	—

Les plaquettes étaient parfaitement isolées des autres éléments [illegible] quarante premières minutes [illegible] au cours de l'exsanguino-transfusion.

et par Fluckiger (10) et a été retrouvé aussi bien au cours des purpura thrombopéniques chroniques qu'aigus en voie de guérison. Il a également été observé au cours des anémies hémolytiques immunologiques (11). La neutralisation de l'antiglobuline par les gamma globulines montre que

la substance anormale fixée aux plaquettes est bien une gamma globuline (tableau IX).

Dans d'autres cas le test de Coombs direct peut être avantageusement

TABLEAU IX

Test de Coombs plaquettaire direct
Neutralisation de l'antiglobuline par les gamma globulines

	ANTIGLOBULINE + DIFFÉRENTES DILUTIONS DE GAMMA-GLOBULINES					
	1/4	1/16	1/64	1/256	1/1000	1/4000
Plaquettes normales	—	—	—	—	—	—
Plaquettes malades	—	—	—	±	++	++
Hématies Rh + sensibilisées par anti D incomplet	—	—	+	++	++	++

remplacé par le test direct de consommation de l'antiglobuline. Entre nos mains ce test s'est montré positif dans plusieurs cas de pancytopénie idiopathique (12).

2° Le test de Coombs plaquettaire indirect a été pratiqué par certains auteurs. Mais ce n'est en fait que son équivalent : la consommation de l'antiglobuline décrite indépendamment par Steffen (14) et par Moulinier (13) qui est utilisable à l'heure actuelle.

Grâce à cette technique il est possible de déceler des substances antiplaquettaires :

— dans le sérum de malades polytransfusés, les résultats sont alors le plus souvent parallèles à ceux obtenus avec la thrombo agglutination à 37 °C ;

— dans le sérum de malades atteints de lupus érythémateux, la réaction étant ici parallèle à celle obtenue avec des leucocytes. Mais aussi — et c'est ici le fait important — dans les sérums de certains purpura thrombopéniques idiopathiques n'ayant jamais reçu aucune transfusion.

Nous nous sommes attachés à étudier les caractères de ces thrombo-anticorps incomplets décelés chez des malades atteints de purpura thrombopénique et jamais transfusés. Leur spécificité antiplaquettaire a été prouvée. Ils sont inactifs sur les leucocytes ; ils sont totalement absorbés sur plaquettes, alors qu'ils ne le sont pas sur leucocytes. Après absorption sur les plaquettes ils peuvent être élués. La réaction est peu influencée par le pH entre le pH 5 et le pH 8. Enfin cette substance se trouve dans les gamma globulines (tableau X).

TABLEAU X

Comparaison des différents « anticorps anti plaquettaires »

	THROMBO AGGLUTININES froides	THROMBO AGGLUTININES chaudes	THROMBO ANTICORPS incomplets (par consommation antiglobuline)
Thermostabilité	+	+	+
Détruit par	10 à 62	5 à 70	
Conservé à — 20	+	+	+
Non absorbable par SO Ba ou $(PO^4)^2Ca^3$	+	+	+
Gamma globulines	+	+	+
Optimum t°	4	37	37°
pH	7 1 à 9 2	6 à 9	6 à 8
ionisation	jusqu à 12 gr o/oo NaCl	jusqu à 12 gr o/oo NaCl	?
Spécificité	Pan agglutinine	Pan ou iso agglutinine	Pan ou iso anticorps
Nature	Inconnue	Iso / Auto } anticorps immuns	Iso / Auto } anticorps immuns

Aussi sommes nous désormais en possession d une technique laborieuse et délicate mais relativement sensible de détection des anticorps incomplets anti plaquettaires

Voici quelques exemples de purpura thrombopéniques non transfusés dans lesquels ces anticorps ont été trouvés

Le premier exemple est celui d une femme de 52 ans atteinte depuis de nombreuses années de purpura chronique et qui possède des thrombo agglutinines froides et des thrombo anticorps incomplets Le test de Coombs direct et le test de consommation de l antiglobuline sont positifs malgré la splénectomie

Un autre exemple de purpura thrombopénique chronique où seul le test de consommation de l antiglobuline est positif Enfin un purpura thrombopénique aigu dans lequel le test de consommation de l antiglobuline s est négativé avec la guérison

6° La dernière variété de thrombo anticorps les **thrombo anticorps allergiques** n agissent qu en présence du médicament

La liste des médicaments connus à l heure actuelle capables de provoquer de telles sensibilisations s établit ainsi la quinine la quinidine le sédormid la sulfa mézathine certains dérivés de l antipyrine l antazoline et peut être les sels d or

Les anticorps allergiques peuvent être décelés aussi bien par la réaction de thrombo agglutination que par la consommation de l antiglobuline

Nous avons étudié plus spécialement le mécanisme des réactions allergiques au sedormid Nos expériences qui font l objet d une communication

séparée témoignent de l importance de l atmosphere qui entoure les pla quettes

Nous avons utilisé des plaquettes lavées huit fois et des plaquettes non lavées C est seulement avec les plaquettes non lavées que le sédormid est

FIXATION DU SÉDORMID SUR L ATMOSPHÉRE PLAQUETTAIRE

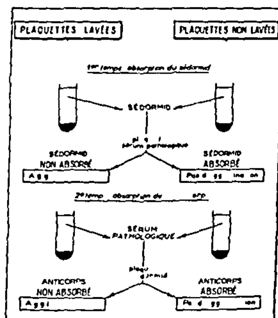


TABLEAU XI — Fixation du sédormid sur l atmosphère plaquettaire

absorbé sur les plaquettes comme le montre l absence d agglutination qui nécessite la présence de sédormid De meme c est seulement sur des pla quettes non lavées et sensibilisées que l anticorps peut etre absorbé Aussi il semble que le complexe antigénique soit forme par le sédormid avec une protéine de l atmosphère plaquettaire et non pas avec une proteine de la plaquette elle meme Ce complexe se forme en l absence de l anticorps (tableau XI)

En conclusion

Les anticorps anti plaquettaires décelables dans les sérums humains sont dirigés soit contre des antigènes de groupe soit contre des antigènes pré sents sur toutes les variétés de plaquettes ou encore *contre des* « allergenes » constitués par les protéines plaquettaires liées à un produit le plus souvent médicamenteux

On peut distinguer aussi des anticorps specifiques inactifs sur les pro pres plaquettes des donneurs, et des anticorps aspecifiques actifs sur toutes les variétés de plaquettes y compris les propres plaquettes des donneurs

1° Des *anticorps spécifiques naturels* qui reagissent avec les antigenes A et B du système ABO

2° Des *anticorps specifiques immuns* qui réagissent avec des antigenes des autres groupes en particulier l antigene D

3° Des *anticorps specifiques immuns* réagissant avec des antigenes de groupe indépendants de ceux des érythrocytes Ce sont les thrombo agglutinines chaudes qui apparaissent à la suite de multiples transfusions Ces anticorps jouent certainement un role dans la survie des plaquettes transfusees et aussi dans l apparition des chocs transfusionnels

4° Des *anticorps aspécifiques froids* (thrombo agglutinines froides) rencontres tres frequemment dans les cirrhoses hepatiques et plus rarement et avec une intensité moindre dans certains purpura thrombopéniques idiopathiques

5° Des *anticorps aspécifiques tiedes* (thrombo agglutinines tiedes actives seulement à température de laboratoire) rencontrees dans deux cas de syndrome hémorragique dont l un seulement thrombopenique

6° Des *anticorps aspécifiques chauds* (anticorps incomplets) que l on peut deceler par la consommation directe ou indirecte de l antiglobuline dans certains cas de purpura thrombopeniques aigus ou chroniques jamais transfusés mais aussi dans le lupus erythemateux disséminé

Ainsi l immunologie des plaquettes a t elle au cours de ces derniers mois fait des progres sensibles qui permettent des nuances sérologiques jusqu ici impossibles et qui laissent esperer que dans un avenir proche nous pourrons faire la distinction biologique entre les purpura thrombopéniques immunologiques et non immunologiques

RÉSUMÉ

Les anticorps anti plaquettaires decelables dans les serums humains sont dirigés contre des antigenes de groupe soit contre des antigenes présents sur toutes les variétés de plaquettes ou encore contre des « allergenes » constitués par les proteines plaquettaires liees à un produit le plus souvent médicamenteux

On peut ainsi distinguer des anticorps spécifiques inactifs sur les propres plaquettes des donneurs et des anticorps specifiques actifs sur toutes les varietés de plaquettes y compris les propres plaquettes des donneurs

1° Des *anticorps spécifiques naturels* qui réagissent avec les antigenes A et B du systeme ABO

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4° Des *anticorps aspécifiques froids* (thrombo-agglutinines froides) rencontrés très fréquemment dans les cirrhoses hépatiques et plus rarement et avec une intensité moindre dans certains purpura thrombopéniques idiopathiques

5° Des *anticorps aspécifiques tièdes* (thrombo agglutinines tièdes actives seulement à température de laboratoire) rencontrées dans deux cas de syndrome hémorragique dont l un seulement thrombopénique

6° Des *anticorps aspécifiques chauds* (anticorps incomplets) que l on peut déceler par le test de Coombs direct par la consommation directe ou indirecte de l antiglobuline dans certains cas de purpura thrombopénique aigu ou chronique jamais transfusés mais aussi dans le lupus erythemateux disséminé

SUMMARY

Platelets antibodies detectable in human sera are either produced by the blood group antigens or by antigens present in all varieties of platelets or by antigens formed by the platelet proteins most frequently combined with a drug

It is therefore possible to discriminate specific antibodies inactive on the host s platelets and specific antibodies active on all varieties of platelets including those of the host

1° Specific natural antibodies which react with the antigens A and B of the A B O system

2° Specific immune antibodies which react with antigens of the other blood groups and specially antigen D

3° Specific immune antibodies which react with antigens belonging to groups independant of the erythrocyte groups

They are hot thrombocyte agglutinines which appear after numerous transfusions These antibodies have an important role in the survival of the platelets transfused but also in the appearance of transfusion shock

4° Non specific cold antibodies (cold agglutinines) are very often observed in liver cirrhosis and seldom in certain forms of idiopathic thrombopenic purpura

5° Non specific tepid antibodies (thrombocyte agglutinines active in ambiant temperature) have been noticed in two cases of hemorrhagic syndroms of which one only was accompanied by thrombopenia

6° Non specific hot antibodies (incomplete antibodies) which can be detected by the direct Coombs test by the direct or indirect consumption of the antiglobulin observed in some cases of acute thrombopenic purpura which have never been transfused but also in disseminated lupus erythematosus

ZUSAMMENFASSUNG

Die in den menschlichen Seren auffindbaren anti thrombozytaren Antikorper sind gegen Gruppenantigene gerichtet entweder gegen bei allen Thrombozytenvarietaten vorkommenden Antigene oder gegen aus Throm

bozytenproteinen die sehr oft mit einem medikamentosen Produkt verbunden sind gebildeten , Allergene

Man kann also unterscheiden zwischen spezifischen Antikorpern inaktiv gegenuber den eigenen Thrombozyten des Spenders und unspezifischen Antikörpern die auf alle Thrombozytenvarietaten inbegriffen die eigenen Thrombozyten des Spenders einwirken

1° *Spezifische naturliche Antikorper* die mit den Antigenen A und B des ABO Systems reagieren

2° *Spezifische Immun Antikorper* die mit den Antigenen anderer Gruppen reagieren, insbesonders mit dem Antigen D

3° *Spezifische Immun Antikorper* die mit Gruppenantigenen reagieren die unabhangig von den Erythrozyten sind Das sind die Warme Thromboagglutinine die infolge zahlreicher Transfusionen auftreten Diese Antikorper spielen sicherlich eine Rolle fur die Überlebensdauer der durch die Transfusion ubertratenen Thrombozyten und auch beim Auftreten von Transfusionsschocks

4° *Unspezifische Kalte Antikorper* (Kalte Thromboagglutinine) die man sehr haufig bei Leberzirrhosen und seltener und in geringerer Intensitat auch bei gewissen idiopathischen thrombopenischen Purpurafallen vorfindet

5° *Unspezifische lauwarme Antikörper* (lauwarme Thromboagglutinine die nur bei Zimmertemperatur wirksam sind) die man in zwei Fallen mit hamorrhagischem Syndrom vorgefunden hat von denen der eine rein thrombopenisch war

6° *Unspezifische Warme Antikorper* (inkomplette Antikorper) die man mit dem direkten Coombstest auffinden kann, durch den direkten oder indirekten Antiglobulinverbrauch bei gewissen Fallen einer akuten oder chronischen Purpura die nicht transfusionsbedingt ist aber auch beim Lupus erythematodes disseminatus

RESUMEN

Los anticuerpos anti plaquetarios que se encuentran en los sueros humanos están dirigidos contra antígenos de grupo contra los que poseen las diversas variedades de plaquetas o contra «alergenos constituidos por proteinas plaquetarias generalmente unidas a un producto medicamentoso Se pueden distinguir entonces anticuerpos específicos inactivos sobre las plaquetas de los dadores y anticuerpos inespecíficos activos sobre toda clase de plaquetas incluso las del propio dador

1° *Anticuerpos específicos naturales* que reaccionan con los antígenos A y B de los grupos sanguíneos

2° *Anticuerpos específicos inmunes* que reaccionan contra los antígenos de otros grupos en particular el antígeno D

3° *Anticuerpos específicos inmunes* frente a antígenos de grupo independientes de los antígenos de los glóbulos rojos Son las tromboaglutininas que aparecen como consecuencia de transfusiones y que con toda seguridad

desempeñan un papel en la aparición de shocks transfusionales y en la sobrevivencia de las plaquetas transfundidas

4° *Anticuerpos específicos fríos* (trombo crio aglutininas) encontrados con frecuencia en las cirrosis hepáticas y mas raremente en ciertas purpuras trombopenicas idiopáticas

5° *Anticuerpos específicos tibios* (activos solamente a temperatura de laboratorio) encontrados en dos casos de síndrome hemorrágico de los cuales uno solamente trombopenico

6° *anticuerpos específicos calientes* (incompletos) que pueden ser evidenciados con el test de Coombs directo en algunos casos de purpura trombopénica aguda o crónica no transfundidas y también en el lupus eritematoso diseminado

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IMMUNOLOGY OF THE LEUCOCYTES*

by

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Although less is known about the immunology of leucocytes than of the other blood cells it is now clear that white blood cells are effective antigens and that some clinical disorders are ascribable to this property Further more present evidence suggests that the following general principles adduced from studies on erythrocytes and platelets are applicable to leuco cytes

1 There are several varieties of antibodies for formed elements of the blood They may be naturally occurring or immune They may be isoantibodies or autoantibodies The latter are prone to develop with especial frequency in certain clinical disorders or as a consequence of expo sure to a number of exogenous agents

2 All formed elements contain some antigens in common But the clinically important antigens in each of the three cell lines are for the most part distinct and detectable only in the cell line affected with a given disorder

3 The *in vivo* consequences of exposure of cells to antibody depend on several factors the cell line involved the abruptness and degree of the insult and the ability of the host to call forth reserves and augment production to keep pace with increased destruction In general the hematologic reflections are peripheral cytopenia and hyperplasia of precursors in the marrow with a notable increase in younger forms however exceptions to these morphologic findings are known to occur

4 Neonatal cytopenia may be due to transplacental transfer of maternal auto or isoantibodies

5 Although the spleen is a site of antibody production and cell destruc tion and splenectomy often ameliorates antibody mediated cytopenia this organ is implicated chiefly as an unwitting bystander in the expression of a more generalized pathologic process In contrast hydrocortisone

* Supported in part by a grant from the USPHS (HF 4889 C 2) and in part from gifts in memory of Mark Ed son Russell Keler Daniel Saxton and Phillip Hunkle

and its derivatives seem to exert their beneficial effects through suppression of antibody formation and stimulation of a further increment in rate of cell production virtually nothing is known about the chemical basis for these actions

In the following discussion each topic will be considered in relationship to the leucocyte and separate reference will be made to febrile transfusion reactions due to white cell antibodies

IMMUNOLOGIC TECHNIQUES

Special problems are presented by the leucocyte when it is subjected to serologic study It is impossible to obtain a preparation free of erythrocytes In addition the white cell population consists of three morphologically distinct and presumably to some extent antigenetically heterogeneous families each containing members of varying age Also there is reason to believe that in certain disorders antibodies for leucocytes may be directed not against the cell membrane but rather against various intracellular components e g the nucleus and cytoplasmic constituents thereby creating a variety of technical problems for their detection Finally white cells tend to adhere to each other due in part probably to the presence of fibrinogen on their surface and under special circumstances to the phenomenon of leukergy The latter is a particularly deceptive cause for spurious results

The procedures which have been devised are numerous attesting to the fact that none is satisfactory for all needs Most widely employed has been *leucocyte agglutination* by test sera (1 6) Its chief advantage is its simplicity it also permits morphologic differentiation of the cellular participants in the reaction The procedure has been applied to the study of hematologic disorders by a number of investigators among them one of my associates Thomas Brittingham Much of the data to be presented will be from his observations

The *antiglobulin consumption* test has been utilized in a number of laboratories principally as a means of detecting incomplete antibodies (7) It is an elaborate procedure time consuming and subject to gross errors in interpretation especially since the variables influencing the content of normal plasma proteins in the leucocyte preparation are not known Even the role of pinocytosis is obscure and challenges the basic premis s of the test

Leucocyte lysis has been used as an index of antibody activity (8) it has the limitation that not all antibodies are lytic under the usual conditions of study

Precipitin reactions (9) *agar gel diffusion* (10) and *immuno electrophoresis* (11) techniques have been employed with some success Much of the present data are preliminary and have at times yielded positive results in states not otherwise suspected nor logically assumed to have an immunologic component

Complement fixation (12) is a standard immunologic procedure but one which has found little application in the detection of antibodies for blood cells

Many other procedures have been devised to detect leucocyte antibodies These include decrease in motility and phagocytosis release of intracellular enzymes vacuolization of cytoplasm and impairment of incorporation of labelled precursors into RNA and DNA (13) All are highly non specific phenomena which must be subjected to careful interpretation Similar limitations apply to *in vivo* assays in experimental animals or human volunteers conducted by either intravenous injection of test plasma or skin testing The body responses to anti leucocyte antibodies are far less predictable than to antibodies against erythrocytes or platelets Indeed it is likely that leucopenia is an inconstant feature of *in vivo* exposure of white blood cells to antibody

Present evidence serves only to tempt speculation but not to establish the scope of immunologic mechanisms in leucocyte pathology Care must be taken to avoid assignment by default to immunology of all unexplained observations But one fact is clear the leucocyte is a fertile subject for study It is structurally more complex than other blood cells and in this respect, resembles most fixed tissues If satisfactory techniques can be devised for the study of all antigenic sites in leucocytes the methods should have wide application in many other systems

VARIETIES OF LEUCOCYTIC ANTIGENS AND ANTIBODIES

Heteroantibodies The first conclusive evidence for the presence of both ubiquitous and distinct antigens in leucocytes was obtained several decades ago (14) Immunization of one animal species with preparations of each of the formed elements of the blood from a second species invariably led to the production of at least four separable antibodies One of these cross reacted with all three cell lines But by appropriate antibody absorption techniques agglutinins specific for each cell line could be prepared (15) These heteroantibodies have been invaluable research tools Recent adaptations have included production of antisera for isolated subcellular constituents of the leucocyte (16 17)

Isoantibodies Antigens identical to those in the erythrocyte have been detected The leucocyte apparently shares some of its antigenic constitution with other cells in the host Well documented are A_1 A and B isoagglutinogens (18 19) Therefore the naturally occuring isoagglutinins a and b are of theoretic clinical importance In practice however as will be pointed out the isoagglutinins unrelated to any red cell antigen are of far greater importance They develop as a consequence of multiple transfusions or pregnancies

Though compatible transfusions induce leucocyte isoagglutination several factors must influence its development It is reasonable to assume that some of the variables are the degree of responsiveness of the recipient his antigenic profile the interval between transfusions and the integrity of the antigens in the transfused leucocytes Undoubtedly there are other unknown influences If at weekly intervals 50 ml of whole blood from a single leukemic donor with a high white cell count are collected without anticoagulant in a siliconed syringe and promptly transfused into a normal volunteer isoagglutinins may be demonstrated at the end of six to nine weeks If no furth

gradually disappears over a period of approximately six months But upon re infusion of a single 50 ml volume of leukemic blood the recipient s isoantibody quickly reappears (20) If bank blood is employed wherein each unit is from a different donor and the leucocytes are fewer in number and not viable more transfusions are generally required to induce leucoagglutinins Most commonly they do not make their appearance until after approximately 20 routine transfusions and thereafter they tend to increase irregularly in frequency potency and spectrum (5 20 21) There have been exceptional instances however in which typical isoagglutinins have been observed following as few as one to four transfusions of bank blood while at the other extreme no leucoagglutinins may be detected even following 100 or more transfusions (20)

In general agglutination of leucocytes is similar in degree whether the cell suspension is obtained from normal donors or subjects with leukemia. Indeed cells from patients with chronic lymphocytic leukemia are usually as readily agglutinated as those from chronic granulocytic leukemia (20 21) There does appear to be less agglutinability of acute leukemic leucocytes however (20 21) In acute leukemia before and after remission a distinct enhancement of agglutination may be noted as the leukemic cell population is replaced by normal white cells (22)

A surprising observation has been that most potent leucoagglutinating sera react equaly well with normal human leucocytes from nearly all donors Whereas red cell and platelet isoantibodies have limited ranges of activity corresponding to a determinable incidence of antigens in the population sampled isoimmune sera for white cells generally possess a broad spectrum of activity Two explanations seem most tenable First leucocytes may contain an extraordinary number of potent antigens and in this sense may be almost as individual as are fingerprints If so then production of multiple antibodies from repeated transfusions of blood from even a single donor to the same recipient could take place and in their aggregate a broad spectrum of isoagglutinins would be produced In this connection it is notable that Brittingham and others have transfused leucocytes obtained from one donor into one recipient at regular intervals and thereby observed the development of a leucoagglutinating serum active against white cells of most individuals Second if only a few critical leucocyte antigens were involved but each was present or absent with random frequency in a mixed population then the likelihood would be great of broad spectrum isoimmunization as a sequel to transfusions from multiple donors In either instance multiple antibodies would be accountable for the progressive range of activity of leucoagglutinins observed following repeated transfusions of blood from the same donor or from many donors Again the greater body of information on platelet and erythrocyte isoimmunization would support this interpretation

Irrespective of their rate of development the agglutinins conform in their characteristics to accepted criteria for isoantibodies They are not active against their host s leucocytes They possess specificity as demonstrated by a consistent pattern of effects on the white blood cells of the same donors tested repeatedly (20 21) and also yield identical results when the cells of monozygotic twins are tested (23) The agglutinin can be absorbed on intact leucocytes separated by elution and reacted with a fresh suspension

of cells Chemical characterization of all leucoagglutinins has not been accomplished but some are beta and gamma globulins (7 23) and are ther moresistant (7)

Although these observations on leucocytes correspond in principle to analogous ones previously made on erythrocytes and platelets one quali fication merits re emphasis Each cell population contains unique anti gens in addition to those common to all the circulating formed elements in a given host Accordingly it is possible to develop erythrocytic pla telet and leucocytic isoimmunization either simultaneously or indepen dently Since methods for determining erythrocytic compatibility are highly developed isoimmunization to the red cell antigens is a relatively uncommon event when contrasted to those of the leucocyte or platelet The isoagglutinogens of these last two cell lines have been subjected to only preliminary examination of their number and incidence It is even now apparent however that selection of blood donors within the frame work of total compatibility for all cells (and plasma proteins) is an impossi bility and ultimate isoimmunization on some parameter from repeated transfusions will continue to be the rule

A corollary of these observations has been the studies on the development of isoimmunization to white blood cells through pregnancy (20 24 25) Present evidence suggests that neonatal agranulocytosis may in some cases at least reflect isoimmunization to leucocytic antigens during pregnancy (24) through a process analogous to that postulated for hemolytic disease of the newborn and some instances of neonatal thrombocytopenia (26)

Autoantibodies Evidence is abundant that certain disorders of erythro cytes and platelets are mediated by antibodies directed against the host s own cells It is reasonable to assume that analogous mechanisms obtain for leucocytes However direct evidence is limited to observations on only a few syndromes as follows

1 A rare instance of idiopathic neutropenia
2 a few examples of leucopenia due to drug sensitivity and
3 disseminated lupus erythematosus

Although *idiopathic neutropenia* is logically suspect virtually all cases studied have been found to have no demonstrable leucocyte antibodies provided the patients have not been transfused With one exception (27) each clinic with an active interest in leucocyte immunology has only one or a very few sera which contain leucoagglutinins effective against the donor s own cells or have been obtained from subjects who had never been transfused or pregnant These data stand in sharp contrast to those for platelet antibodies in idiopathic thrombocytopenia This lack of serologic confirmation has strengthened the concept that in most instances idiopathic neutropenia may be a reflection of some non immunologic process Howe ver the inadequacy of present day techniques must be considered in any judgement

A host of *drugs and chemicals* are known to cause leucopenia Those which show no selectivity for a given cell line and typically produce marrow aplasia perhaps damage by direct toxic action on the most primitive pre cursor of all formed elements Immunologic injury by benzol for example seems most unlikely On the other hand many agents do show speci ficity for cell lines and some may induce leucopenia unassociated with ane

mia or thrombocytopenia It is not surprising that in those instances of selective leucopenia due to drugs an antibody drug leucocyte interaction has been sought Only two drugs have been clearly incriminated amino- [illegible] vidence for a single ins [illegible] also it has been claimed [illegible] and sulfathiazole may be responsible (27)

Here too the well studied mechanism of drug induced thrombocytopenia affords a basis for investigation of drug induced agranulocytosis (30) The analogous process may be visualized in the following sequence formation of an antigenic complex of drug and leucocyte which in the susceptible host incites antibody production with consequent leucocyte destruction But again in contrast to the numerous documented examples of platelet supression on this basis stands the sparsity of evidence for drug or chemical causation of leucopenia via immunologic means When this experience is coupled with the clinical experience that drug induced agranulocytosis often reflects protracted exposure to large doses of the offending agent a rational basis is afforded for the postulate that some metabolic handicap through a biochemical lesion rather than an immunologic mechanism may mediate the cytopenia Genetically determined susceptibility of erythrocytes to a group of related aromatic compounds (31) has been cited as a prototype for this concept (32)

Lupus erythematosus is in one sense an immunologic paragon for herein ready immunization is remarkably common at least at the clinical level Agranulocytosis is not a feature nevertheless there is reason to suspect that a unique immunologic mechanism may involve the leucocyte in the genesis of the LE cell phenomenon The evidence may be summarized as follows The ability of serum from an affected patient to induce LE cell formation can be abolished by absorption on cell nuclei obtained from any animal source (33) Furthermore pre treatment with nucleoprotein itself will often suffice and even the use of desoxyribonucleic acid alone may at times be adequate (34) Desoxyribonuclease abolishes the capacity of nuclei to adsorb the LE factor From these data alone it would seen premature to assign the LE phenomenon to an immunologic category but more acceptable criteria may be cited Complement fixation can be demonstrated with isolated nuclei and LE serum and the degree of complement fixation generally parallels the capacity of the serum to induce the LE cell phenomenon (34) Therefore some interrelationship between immunology and the LE phenomenon seems probable However it has now been shown that the factor responsible for LE cell production is separable from the complement fixing activity and therefore an immunologic basis for both cannot be adduced (34) It may be concluded nevertheless that LE serum contains antinuclear factors some of which fix complement and are accordingly most probably antibodies Their relationship to the pathogenesis of disseminated lupus erythematosus is not known

Worthy of mention although additional corroboration is needed is the observation that leucoprecipitins may be found in the serum of some *leukemic subjects* (7) Whether or not these are autoantibodies and if so their significance remains to be established Perhaps the leukemic cell is regarded by the host as an antigenic alien

TRANSFUSION REACTIONS DUE TO IMMUNIZATION TO THE BUFFY COAT

Several years ago it was noted that plasma from patients with circulating antibodies for platelets could induce fever and malaise when administered to normal recipients (35) When plasma which contained in addition white cell antibodies much smaller quantities were capable of inducing even more profound reactions (36) Brittingham has devoted the past four years to a study of leucocytic antibodies and has been especially interested in these non hemolytic transfusion reactions His clinical material has been derived from over 1200 subjects half of whom were normal individuals and half patients with leucopenia from a variety of causes dysproteinemia or a history of multiple transfusions or pregnancies No leucoagglutinins were found in his control sera whereas 70 members of the patient group had clear cut white cell antibodies (Table I) Nearly

TABLE I

Date on incidence and variety of leucoagglutinins The isoagglutinins were characterized by failure to react with the donor s own leucocytes The unidentified agglutinins were not classified due to failure or inability to test against the donor s own leucocytes to exclude spurious agglutination by dysproteinemia or to establish a rare instance of probable autoagglutination

SEROLOGIC RESULTS

	Negative	Positive	Isoagglutinin only	Undefined Agglutinin
Normal Controls	601	0	0	0
Patients	539	70	35	35

all were individuals who had had numerous transfusions and in general the most potent antibodies were noted in sera from patients in whom unexplained febrile transfusion reactions were prone to occur (37)

At great risk to himself Doctor Brittingham has succeeded in establishing the pathogenesis of these reactions His conclusions may be summarized as follows First though pyrogenic reactions occur from platelet antibodies they are far milder than those due to leucocyte antibodies Second distressing buffy coat reactions are common in the multitransfused subject and are most often attributable to the white blood cells administered Third and of greater importance disastrous consequences may follow transfusion of whole blood or plasma from a buffy coat immunized donor into a normal recipient The first and second reactions can be circumvented by removal of the buffy coat prior to transfusion a manipulation easily accomplished by centrifugation with plastic donor equipment or dextran sedimentation of erythrocytes (38) No feasible means

is available for averting the last the passively induced (and more dangerous) reaction Here therefore is another reason for rejection of the blood donor who has himself received many transfusions Previously the dangers of serum hepatitis and erythrocyte and platelet isoimmunization were documented Leucocyte isoimmunization is also a hazard

What are the features of the second and third reactions? Shown in figure 1 is a typical temperature response curve to infusion of the buffy

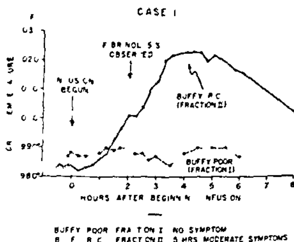


FIG 1 — Typical febrile response to infusion of buffy coat in a leucocyte-immunized recipient Notable are the latent period before onset of the reaction and the failure of whole blood from which the buffy coat has been removed to induce any untoward effects (Figure reproduced by permission of the Journal of the American Medical Association)

coat rich fraction in a leucocyte immunized recipient Note that approximately one hour elapsed before the onset of the febrile response thereupon the recipient experienced shaking chills fever prostration backache nausea and vomiting No reaction followed the administration of a buffy coat poor preparation of the same blood As its corollary when only 35 ml of plasma from a subject strongly immunized to leucocytes was given to a normal recipient a more profound syndrome developed within 20-30 minutes This was characterized by severe chills fever dyspnea cyanosis hypotension bronchospasm widespread patchy pulmonary edema electrocardiographic aberrations and extreme prostration The syndrome lasted for many hours and was followed in one instance 10 days later by serum sickness Infusion of larger quantities of the same plasma would unquestionably have been promptly lethal

Hematologically a transitory severe leucopenia lasting less than two hours and followed promptly by marked neutrophilic leucocytosis was regularly observed in the isoimmunized recipients of buffy coat while in the recipient of leucoagglutinin containing plasma the leucopenia tended to last even longer (Figure 2)

A discussion of the pertinence of these observations to the pathogenesis of fever due to endogenous pyrogen is beyond the scope of this discussion

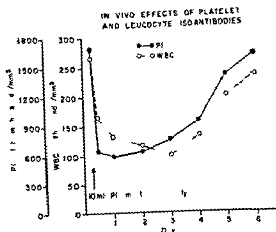


FIG 2 — Hematologic effects of injection of 10 ml of plasma from a subject strongly isoimmunized to leucocytes and platelets into a patient with chronic granulocytic leukemia The donor had received approximately 600 transfusions for anerythrocytogenic anemia

It is appropriate however to re assert that most instances of non hemolytic febrile transfusion reactions must now be considered due to leucocyte isoimmunization

DISCUSSION AND CONCLUSION

The leucocyte is a potent antigen Nearly all of the applications of immunology to the erythrocyte and platelet have now been documented for the white cell The white cell may have heteroantibodies isoantibodies and autoantibodies In appropriate instances antibodies for white cells cause leucopenia in their hosts neonatal leucopenia in infants born to mothers who have white cell antibodies and leucopenia in recipients who passively receive them In addition in part probably related to its content of endogenous pyrogen immunologic damage to leucocytes *in vivo* is associated with febrile reactions these may have alarming concomitant manifestations with predominantly pulmonary localization Finally a challenging though incompletely defined relationship now seems likely between the LE phenomenon and immunologic processes

A totally unexplored area in leucocyte immunology is that concerned with the role of the spleen and the possible usefulness of steroids in the management of autoimmune agranulocytosis *A priori* one would expect that hydrocortisone and its analogues would be highly effective since these agents suppress antibody formation and are potent enhancers of neutrophil

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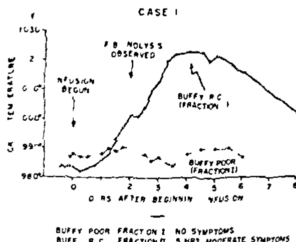


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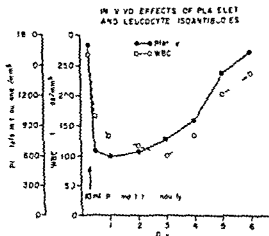


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production Less probable would be the value of splenectomy since the available data tend to implicate the lungs as the major site of initial sequestration of damaged leucocytes (39 40) However, adequate evaluation of these therapeutic approaches has not been carried out as stated earlier autoimmune neutropenia by present assessments is a very rare disorder

It is tempting nevertheless to speculate upon the reasons for development of autoimmunity Any theory, however valid probably does not explain all instances First autoantibodies may in appropriate instances represent host reaction to antigenic alteration of his own tissues by drugs chemicals and perhaps other agents Acceptable evidence has been documented for this mechanism in disorders of each of the three formed elements of the blood Second the host may produce antibodies against an exogenous invader for example, the A like substance in the Type XIV pneumococcus with consequent hemolytic anemia if the individual is of blood group A Or more commonly he may generate antibody against an endogenous enemy for example a neoplasm may incite formation of antibodies which cross react with the tumor and an antigenically similar though innocent bystander of a blood cell line (41 42) A third possible sequence is attractive though unproved Complementariness of molecular structure is thought to be essential for antigen antibody interaction It seems reasonable to speculate that in some disorders particularly those prone to give bizarre serologic reactions (e g lupus erythematosus) protein molecules with a fortuitously complementary configuration may be elaborated Finally clones of cells may develop either by stimulus or *de novo* which could have one of two properties They might have the ability to produce antibody like proteins which are also fortuitously complementary to certain host antigens or the cells themselves might be genetically different and thereby regard certain host antigens as foreign and generate quite deliberately host specific antibodies

A final word of caution is in order Very little substantial proof has been obtained that most leucopenias whether idiopathic or attributed to disease drug or chemical are mediated by immunologic means Present evidence suggests that only the exceptional case is due to antibodies for leucocytes and that more often some other pathogenesis may be accountable

SUMMARY

A number of immunologic properties have been defined for white cells

1° Leucocytes possess certain *antigens* in common with other formed elements notable are A B M and N For the most part however the clinically important antigens appear to be distinct from those in other host cells

2° There are several *varieties of antibodies* for leucocytes naturally occurring and immune complete and incomplete and isoantibodies and autoantibodies Under appropriate conditions various of these may induce leucocyte agglutination lysis precipitin reactions complement

fixation and numerous non specific evidences of cellular injury Electrophoretically most of the antileucocyte factors reside in the beta and gamma globulin moieties

3° The *in vivo hematologic reflections* of response of white blood cells to their antibodies vary from absence of discernible alteration to profound leucopenia with either hyperplasia or depletion of white cell precursors in the bone marrow

4° In the *causation of disease* leucocyte antibodies have been implicated in agranulocytosis due to certain drugs (especially aminopyrine and sulfapyridine) in non hemolytic pyrogenic transfusion reactions in neonatal leucopenia (due to transplacental transfer of maternal antibodies active against fetal leucocytes) and in an occasional instance of leucopenia either of the idiopathic variety or as ociated with another disorder

Less clear is the nature of the complement fixing antinuclear factor of LE serum and the leucoprecipitin found in some leukemic sera

Care must be taken to avoid assignment of all unexplained depressions of leucocyte levels to immunology by default There is acceptable evidence which relates immunologic processes to some instances but there is also reason to suspect that other mechanisms may be of even greater importance in most leucopenic states

RÉSUMÉ

On a decrit un certain nombre de propriétés immunologiques des leucocytes

1° Les leucocytes possedent certains antigenes qui sont communs aux autres élements figurés du sang notamment les antigènes A B M et N Cependant pour la plupart des phénomenes cliniques les antigenes leucocytaires semblent etre differents de ceux contenus dans les autres cellules de l hote

2° Il existe plusieurs variétes d anticorps diriges contre les leucocytes anticorps naturels et immuns anticorps complets et incomplets iso et auto anticorps Suivant les conditions certains d entre eux peuvent provoquer l agglutination la lyse la reaction de précipitation la fixation du complément ainsi que de nombreux aspects de lésions cellulaires non spécifiques Au point de vue electrophorétique la plupart des facteurs antileucocytaires sont situés dans les fractions globuleniques beta et gamma

3° La reponse hématologique *in vivo* de la réaction entre les leucocytes et leurs anticorps se traduit soit par l absence d alterations visibles de ces cellules soit par une profonde leucopénie avec une hyperplasie ou une diminution du nombre des cellules méres de la moelle osseuse

4° Dans la détermination de la maladie les anticorps antileucocytaires sont responsables de cas d agranulocytose provoqués par certains médicaments (spécialement pyramidon et sulfapyridine) de réactions transfusionnelles pyrétogenes et non hémolytiques de leucopénies chez les nouveau nés (par passage transplacentaire d anticorps maternels actifs contre les leucocytes du fœtus) et de certains cas de leucopenie soit idiopathique soit associée avec d autres troubles

Moins facile a comprendre est la nature des facteurs anti nucleaires du serum L E qui fixent le complément ainsi que celle des leucoprécipitines trouvées dans certains sérums leucémiques

Il faut prendre garde d attribuer par défaut d explication toute leucopenie à des processus immunologiques Il y a un certain nombre de faits qui permettent de relier le phénomene a des causes immunologiques mais il y a aussi des raisons de suspecter que d autres mécanismes non immunologiques jouent un role plus important dans la plupart des états leucopéniques

ZUSAMMENFASSUNG

Eine Anzahl von immunologischen Eigenschaften wurden fur die weissen Blutzellen genau bestimmt

1° Leukozyten besitzen gewisse *Antigene* gemeinsam mit anderen geformten Elementen bemerkenswert sind A B M und N Meistenteils jedoch scheinen die klinisch wichtigen Antigene von denen der anderen Wirtszellen verschieden zu sein

2° Es gibt gewisse *Antikorpervarietäten* gegen Leukozyten naturlich vorkommende und immune komplette und inkomplette Iso- und Autoantikorper Unter besonderen Bedingungen durften manche davon Leukozytenagglutination — Lyse — Prazipitinreaktionen — Komplementbindung und verschiedene andere unspezifische Zeichen einer Zellschadigung bedingen Elektrophoretisch konnten die meisten antileukozytaren Faktoren in den Beata und Gammaglobulinen lokalisiert werden

3° Die *hamatologischen Ruckwirkungen in vivo* der Antwortsreaktion der weissen Blutkorperchen mit ihren Antikörpern variieren vom Fehlen sichtbarer Veranderungen bis zur ausgepragten Leukopenie mit entweder Hyperplasie oder Erschöpfung der Vorstufen der weissen Blutkorperchen im Knochenmark

4° In *ursachlichen Zusammenhang mit Krankheiten* wurden Leukozytenantikorper bei durch gewissen Medikamenten (besonders Aminopyrin und Sulfapyridin) hervorgerufenen Agranulozytosen gebracht ebenso bei nicht hamolytischen pyrogenen Transfusionsreaktionen bei neonataler Leukopenie (bedingt durch transplazentare Übertragung mutterlicher Antikorper gegen fetale Leukozyten) und bei gewissen Fallen von entweder idiopathischer oder mit anderen Storungen gekoppelter Leukopenie

Wenig klar ist die Natur des komplementfixierenden antinukleären Faktors von LE Seren und des Leukopräzipitins das in manchen Leukamieseren gefunden wird

Man muss aber darauf achten nicht alle ungeklarten Senkungen des Leukozytenspiegels mit der Immunologie in Zusammehnang zu bringen Es bestehen in manchen Fallen begrundete Beweise fur das Verantwortlichsein immunologischer Prozesse aber es bestehen auch Grunde bei den meisten Leukopenien anderen Mechanismen eine grossere Bedeutung beizumessen

RESUMEN

Los glóbulos blancos presentan una serie de propiedades inmunologicas

1º Poseen ciertos *antígenos* comunes con otros elementos notablemente A B M y N aunque los antígenos clinicamente importantes son diferentes

2º Existen *varias clases de anticuerpos* anti leucocitos naturales inmunes completos e incompletos isoanticuerpos y autoanticuerpos Segun las condiciones pueden producir aglutinacion lisis precipitación fijacion de complemento y numerosos tipos de lesion celular Electroforeticamente todos estos anticuerpos estan en las beta y gama globulinas

3º Las *consecuencias hematologicas* de la accion de los anticuerpos sobre los leucocitos pueden ir desde una aparente inocuidad hasta una intensa leucopenia

4º Como *agentes causales* los anticuerpos antileucocitos estan implicados en las agranulocitosis debidas a ciertas drogas (especialmente aminopirina y sulfapiridina) en reacciones de transfusión no hemolíticas en la leucopenia neonatal (debido a pasaje placentario) y ocasionalmente en leucopenia ya sea idiopática o asociado con otro trastorno

La naturaleza de la sustancia antinuclear que fija complemento en el suero LE y de la leucoprecipitina de algunos sueros leucemicos no se conoce suficientemente

Debe tenerse cuidado de no atribuir un mecanismo inmunologico a todos los trastornos leucocitarios en la mayoría de los casos existen otros mecanismos de mayor importancia

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DISCUSSION

par

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Nous nous bornerons à résumer quelques uns des résultats obtenus au cours des études sur la constitution antigénique des leucocytes et les anti-corps anti-leucocytaires que nous poursuivons depuis plusieurs années.

1. Antigènes des leucocytes

Par la technique de double diffusion en milieu gélifié d'Ouchterlony, *il est possible de démontrer l'absence dans des extraits de leucocytes humains* correctement lavés des principaux constituants protidiques du sérum, en *particulier sérumalbumine et γ globulines. Nous avons ainsi constaté que* les lymphocytes (normaux ou leucémiques) du sang ne contiennent pas de *constituants possédant la spécification antigénique des* γ globulines du sérum.

Par ces mêmes techniques, il nous est possible actuellement, à l'aide de puissants immunsérums anti-leucocytaires, d'identifier dix à onze anti-gènes leucocytaires solubles en milieu isotonique. Ce nombre est sûrement très faible par rapport à la réalité. De plus, ces extraits de leucocytes normaux sont préparés à partir de suspensions comprenant à la fois des poly-nucléaires et des cellules mononucléées, car il nous a été impossible d'obtenir une préparation pure de chacune de ces variétés en quantité suffisante.

Par l'immuno-électrophorèse, on peut préciser la mobilité électrophorétique d'un grand nombre de ces constituants antigéniques des leucocytes normaux. C'est ainsi qu'ont actuellement été identifiés : un constituant dont la mobilité est nettement supérieure à celle de la sérumalbumine, trois constituants au moins migrant comme des α globulines, une β_1 globuline; deux β globulines et deux constituants ayant la mobilité des γ globulines. *Il faut insister sur le fait que si l'on prend comme référence la mobilité* électrophorétique des protéines du sérum, ces antigènes leucocytaires ont une spécificité antigénique différente de celle des protéines sériques de même mobilité électrophorétique.

Dans cette étude analytique des antigènes leucocytaires, nous nous efforçons d'adjoindre à cette double caractérisation (selon la spécificité antigénique et selon la mobilité électrophorétique) les deux caractérisations suivantes : situation dans la cellule de chacun de ces antigènes et nature chimique.

La comparaison entre la constitution antigenique des leucocytes normaux et celle des leucocytes le [illegible] ficultés des que l on cherche [illegible] presence dans l une des [illegible] constituant totalement absent dans l autre Nous constatons l augmentation considérable dans les granulocytes leucémiques d une fraction de mobilité γ globulinique et d une β_2 glycoprotéine mais il semble s agir de différences quantitatives S il existe une différence qualitative nos expériences plaideraient en faveur de l absence de certains antigenes dans les leucocytes leucémiques Peut etre est elle liee à l immaturité de ces cellules peut etre temoigne t elle d un défaut fondamental de la synthèse protéique dans les cellules malignes comme cela semble etre le cas pour les γ globulines anormales produites par les plasmocytes malins du myelome ?

II ANTICORPS ANTI LEUCOCYTAIRES

Les techniques de précipitation et de fixation du complement peuvent etre utilisees avec succes dans la recherche de ces anticorps Il ne faut pas perdre de vue que selon la technique et la nature du matériel antigenique utilise (cellule entiere extraits préparés selon differentes modalites résidu insoluble poudre leucocytaire) l immuno hématologiste peut déceler des anticorps differents Il faudrait s efforcer de définir l antigene leucocytaire avec lequel reagit un anticorps c est ainsi qu a pu etre identifié l anticorps anti D N A du lupus érythémateux disseminé dont il est question ailleurs (voir p 558) Au cours de cette affection on peut également trouver dans le sérum outre d eventuels iso anticorps post transfusionnels des anticorps anti leucocytaires réagissant avec d autres antigenes que le D N A Dans quelques cas de leucoses aigues non encore transfusées on peut trouver des anticorps sériques anti leucocytaires leur incidence est faible Il s agit surtout de leucoses à monocytes Nous n avons jamais constate la présence d anticorps anti leucocytaires au cours des neutropénies idiopathiques rejoignant ainsi les conclusions de Harrington

Il est possible que d éventuels auto anticorps anti leucocytaires echappent à nos investigations non seulement ils pourraient etre fixés sur les leucocytes mais encore ils pourraient se combiner aux antigenes leucocytaires présents dans le sérum

III *ANTIGENES LEUCOCYTAIRES DU SÉRUM*

Les méthodes immunochimiques nous ont permis de démontrer la présence dans le serum humain normal à concentration tres minime de certains des antigenes leucocytaires solubles en milieu isotonique Le principal de ces antigènes est le meme dans tous les serums normaux examinés il s agit d une α globuline leucocytaire présente dans toutes les varietés de leucocytes normaux et leucémiques

La teneur du sérum en antigenes leucocytaires a ete étudiée dans les différentes variétés de leucemies elle est variable dans les leucoses aigues abaissée dans la leucémie lymphoide chronique tres élevée dans la leucémie myeloide chronique ou l on trouve a forte concentration des antigenes leucocytaires plus nombreux que dans le sérum normal

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STUDIES ON EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS (*)

by

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Much recent interest has centered around a group of clinical and experimental diseases the etiology and the pathogenesis of which are thought to involve auto allergic mechanisms Among these diseases may be included experimental allergic encephalomyelitis a disease simulating in many pathological features postvaccinal and postinfectious encephalomyelitis in man (1 4) The auto allergic hypothesis has also been invoked to explain the occurrence of acquired hemolytic anemia (5) essential thrombocytopenic purpura (6) certain acquired neutropenias (7) infectious polyneuritis (6) the Guillian Barre Syndrome (9) sympathetic ophthalmia (12 13) phacoanaphylactic endophthalmitis (10 11) aspermatogenesis (14) and thyroiditis (15) In each of these instances substantial evidence often through the agency of a workable experimental model has been brought foreward indicating that the basis of the disease rests upon an auto allergic mechanism In none of them save autoimmune hemolytic anemia of man (16 18) has the operation of an autoimmune process been proved However the apparent demonstration of the operation of autoimmune processes in experimental and clinical disease has led to implication of auto allergic hypothesis concerning the etiology and pathogenesis of numerous other poorly understood diseases of man Included in this latter group are such problems as rheumatic fever rheumatoid arthritis chronic nephritis cirrhosis of the liver lupus erythematosus and other collagen diseases (19)

Consequently it is our view that the value of experimental allergic encephalomyelitis to medical science lies both in its usefulness as a model for studying demyelinating and inflammatory processes within the central nervous system and also perhaps more importantly as a model for studying the nature of autoimmune disease in general (20)

( ) Aided by grants from the U S P H S American Heart Association Minnesota Division of the American Cancer Society and Minnesota Heart Association

This experimental disease (E A E) has been the subject of intensive investigation for more than 20 years Today E A E is under investigation in numerous laboratories and progress is being made toward the elucidation of the etiologic agent and in characterizing the pathogenetic mechanism Although demyelination occurs as a regular concomitant of this disease which is expressed in greater or lesser degree in all experimental animals studied it is our view that when demyelination does occur in this disease it is only one component of a general host reaction initiated by parenteral administration of central nervous tissue In the development of E A E it is the reaction of the host to the encephalitogenic agent in nervous tissue which must be emphasized It is this specific reaction to homologous heterologous or even autologous nervous tissue which leads to inflammation demyelination and clinical disease

It is the purpose of this report to review briefly the history of this experimental disease review the evidence indicating its allergic nature review studies indicating the nature of the encephalitogenic material and its location within the central nervous system to describe methods found effective in preventing or altering the course of E A E to describe the sequence of changes in lymphoid tissue preceding development of the disease to define the early pathological changes in the central nervous tissue as revealed by study with both light and electron microscope and finally to describe studies using autotransplants of lymphoid tissue into the brain which we interpret to support the view that there exists an antigen in brain tissue which provokes a response in autologous mesenchymal tissue

HISTORICAL REVIEW

The earliest observations of acute allergic encephalomyelitis were probably made in man consequent to efforts to immunize against rabies with vaccines [illegible] That disseminated ence

ns of normal nervous

d wasting sometimes

occurred after injection of animals with suspensions of normal brain (17) and paralytic episodes occasionally occurred in animals receiving repeated injections of normal nervous tissue (26 27) Koritschoner and Schweinberg (28) concluded from a review of the literature together with their own observations that injection of normal nervous tissue in rabbits occasionally produced a disease strikingly similar to post immunization paralysis occurring after anti rabies treatment

The lack of reproductibility of this model (29) the failure often to separate the disease produced from known parasitic infections (30) detracted from the significance attached to these observations However the recognition that acute disseminated encephalomyelitis featured by perivascular and perivenular demyelination occasionally followed acute exanthematous diseases (31) and smallpox vaccination (32 33) provoked Rivers et al (13) to compare pathological features of vaccinal infection in monkeys and acute disseminated encephalomyelitis in man They concluded that vaccinal encephalomyelitis was different morphologically from acute disseminated

encephalomyelitis These authors then showed that repeated injections of normal brain tissue over a period of many months resulted in the development of disseminated encephalomyelitis with perivascular demyelination Rivers and Schwentker (34) repeated the studies and reported that injections of nervous tissue emulsions and extracts over a long period regularly produced pathologic changes in the nervous system of monkeys accompanied by demyelination They concluded that their observations represented the experimental counterpart of the central nervous system accidents occurring during Pasteur anti rabic treatment Their studies appeared to establish that foreign nervous tissue was the etiologic agent in the disease under study

These observations confirmed by Ferraro and Jervis (35) required numerous injections of brain tissue over a prolonged period and the experimental model was too unwieldy for general use However I Morgan (36) and Kabat Wolf and Bezer (37) independently and simultaneously found that acute disseminated encephalomyelitis could regularly be produced with but a single injection of brain tissue incorporated in the adjuvants of Feund and McDermott (38) Further the incubation period for the experimental disease was reduced from many months to a period of less than 30 days Confirmation of these important observations was immediate and in a short time this experimental encephalopathy had been extended to the guinea pig (39) rabbit (40) dog (41) mouse (42) rat (43) and cat (44)

Extensive pathological studies have been carried out on animals developing central nervous system disease following injection of central nervous tissue in adjuvants although considerable variation has been observed from animal to animal and laboratory to laboratory the lesions generally described have included meningeal inflammation and thickening perivascular and diffuse inflammatory reactions scattered throughout the central nervous tissue mo t prominent around capillaries and small veins histiocytic and plasma cell accumulation giant cell formation hemorrhagic necrosis and demyelination (1 35)

ROLE OF ALLERGY IN E A E

In spite of intensive investigation of this readily reproductible laboratory model the exact etiology and pathogenetic mechanism have not been established Accumulated data support the view that an immunologic response or allergic reaction is responsible for the development of this experimental disease These observations may be summarized as follows

1 Repeated parenteral injections of suspensions of brain tissue are required for production of the experimental model (33 35) no untoward reaction follows immediately or soon after an initial injection of nervous tissue Instead an initial delay after injections of nervous tissue exists during which it is presumed that an allergic reaction occurs and the disease begins as a violent widely distributed rapidly progressive inflammatory and demyelinating process anatomically related to the location of capillaries and venules of the central nervous system

2 The encephalomyelitis is specifically induced by injection of central nervous tissue and cannot be produced by injections of emulsions of other organs and tiss[illegible]

3 No bacterial or virus agent to account for the inflammatory pathology can be isolated from the central nervous tissues during periods of active disease (34 37 39 48)

4 The intra dermal route of administration of antigen generally results in greater production of antibody and greater tendency to develop hyper sensitivity than does the subcutaneous intra peritoneal or intravenous route of injection (47) In rabbit guinea pig and rat (43 51 51) the intradermal route has resulted in maximal incidence of disseminated encephalomyelitis

5 The use of the immunological adjuvants of Freund not only accelerates the development of encephalomyelitis but markedly increases the incidence of the disease in all species studied

6 The time interval following injection of brain adjuvant emulsion and the subsequent development of disseminated encephalomyelitis is 2 4 weeks a period optimal for production of antibody or development of hypersensitivity (52 53)

7 Immunologically mature animals must be employed in order to obtain a high incidence of disease (54 56)

8 The development of cutaneous allergy of the delayed type is associated with the development of disseminated encephalitis (57 58)

9 Heterologous homologous and autologous nervous tissue components are antigenic since it has been shown that circulating antibodies may be produced following parenteral injection of brain adjuvant emulsions (59 60) The antibodies thus far studied however have nothing to do with the development of the disease (61)

10 The cellularity of the inflammatory process in the brain and spinal cord has been likened to that observed with immunological ereactions in other tissues (43) for example the Arthus reaction in connective tissue (62, 63)

11 Prevention of E A E has been achieved by a number of agents capable of preventing allergic reactions or inhibiting the immune respon e (48 64 65)

12 Passive transfer of the encephalitogenic factor has been achieved employing the technique of parabiotic union in rats

Although absolute proof is not yet available it appears to most workers that the best working hypothesis is that experimental disseminated encephalomyelitis has an immunological basis Detracting from the abundant indirect evidence indicating that disseminated encephalhomyelitis is an allergic disease have been the repeated failures to pas ively transfer the disease with serum peripheral cells or lymphoid cells However the observations of Lipton and Freund (66) indicate that pa sive transfer of the disease can be achieved by parabiosis

Considerable discussion has centered around the type of allergy involved in development of E A E however no clear evidence has been brought foreward establishing whether the central nervous system disorder is due to circulating antibody delayed allergy, wheal and erythema type allergy — combination of these or possibly another as yet unrecognized allergic

formed against compo

ection are not involved

THE NATURE OF THE ENCEPHALITOGENIC FACTOR

It is clear from available evidence that the encephalitogenic factor is present in the central nervous system and less regularly in the peripheral nervous system (36 65 67) Peripheral nervous tissue adjuvant emulsions produce central nervous system disease in the guinea pig but not in monkeys rabbits or mice To the contrary rabbits and mice develop an experimental allergic neuritis when injected with emulsions containing peripheral nervous tissue Extensive injections of emulsions of other organs and tissues fail to produce either encephalitis or neuritis in guinea pigs rabbits or monkeys (8 9)

Considerable evidence indicates that the antigen is located primarily in the white matter (36 65 68) Although efforts to isolate and identify the encephalitogenic agent have been largely unsuccessful it is of interest that reports of progress in identifying the antigen have appeared First it has been reported by Olitsky et al (69) that certain proteolipid fractions (70) contain the antigen However Waksman (71) has pointed out that none of these fractions is more active than crude nervous tissue In addition a preliminary report by Kies et al (72) suggests that an electrophoretic and ultracentrifugally homogeneous collagen like protein from the brain has a high degree of encephalitogenic activity However these studies also contain a discouraging note namely that whole spinal cord antigen regularly produces a higher incidence of maximal disease than do the highest effective concentrations of the mucoprotein antigen It is because of the controversy existing with respect to the effectiveness of the purified antigens that we have chosen to use whole spinal cord emulsified in the complete adjuvant of Freund as the antigen in all of our experiments

PREVENTION OF E A E

The first demonstration that E A E could be prevented was presented by Good et al (48) who found that both very large doses of salicylates and salicylates combined with P A B A would prevent the development of the disease in guinea pigs No therapeutic effect was demonstrated Subsequently A C T H and cortisone (65 73 74) were also found to be preventive In most of the studies no therapeutic effect could be demonstrated However Gammon and Dilworth (75) giving large doses of corticotrophin within 24 hours after the onset of paralysis were able to show a striking therapeutic effect on the disease in guinea pigs These experimental studies have been interpreted as a basis for use of these drugs in treating non infectious acute disseminated encephalopathies in man The most impressive of these studies is a report by Allen (76) whose uncontrolled observations suggest that adrenal steroid therapy is beneficial in treatment of postmeasles encephalitis

Freund and Lipton (77) observed that the local inflammatory reaction at the skin site is not essential to the development of the experimental disease when they excised the antigen depot in the skin as early as three

hours after injection and did not prevent the development of disease This observation might be interpreted to indicate that the intradermal route is of importance in development of the disease not because of any inter reactions of antigen with skin or because of the local inflammation induced in skin but more likely because an intracutaneous injection is in reality an intralymphatic injection (78) and the process essential to development of the disease occurs in the lymph nodes or lymphatics of the body

EXPERIMENTAL RESULTS

All of our studies were carried out in either mature guinea pigs of the Hartley strain or in mature albino hybrid rabbits weighing 2 5 to 3 kilo grams The antigen used was prepared from whole rabbit or bovine spinal cords emulsified in a modification of the adjuvants of Freund and McDermott The antigen emulsions were injected into the pads of the hind feet of the rabbits and intracutaneously in the guinea pigs The majority of animals developing neurological disease showed signs and symptoms within 20 days following spinal cord adjuvant injection and the great majority of animals dying of the disease had died within 30 days Therefore most experiments were terminated 30 days following the intradermal injection of encephalitogenic material Although paralysis was often the predominant manifestation most of the involved rabbits showed signs and symptoms of encephalitis as well Histological studies were regularly carried out using H and E staining of formalin fixed material and methyl green pyronine staining of alcohol fixed tissue

PREVENTION OF E A E BY INJECTION OF AQUEOUS SUSPENSIONS OF BRAIN

In an effort to prevent E A E by classical desensitization daily subcutaneous injections of 50 milligrams of homologous spinal cord in saline beginning on the day of injection of brain adjuvant emulsion and continuing for 20 days did not interfere with the development of E A E. For example 91 % of the group being desensitized developed paralysis whereas neurological signs were observed in only 75 % of controls However the mortality in the treated group was somewhat lower than that in the control group 27 % vs 41 p % This observation suggested that perhaps pretreatment with homologous central nervous tissue over a prolonged period might prove more effective than the relatively brief series of injections of saline suspensions of spinal cord as used in these experiments

Prior attempts to prevent development of E A E by pretreatment with aqueous suspensions of brain tissue had failed (79) However some protection was demonstrated by pretreatment with emulsions of brain tissue in oil without the tubercle bacilli (80) In this study rabbits in the experimental group received two courses of immunization with saline suspensions of spinal cord In each course 80 100 milligrams of spinal cord

were administred in each of four subcutaneous sites at weekly intervals A test period of approximately two months separated the two courses Thus each rabbit was given a total of 2 5 grams of spinal cord suspended in saline To control a non specific effect of a depot containing large quantities of nervous tissue another group of rabbits received a single subcutaneous injection of 2 4 grams of fresh rabbit cord in saline on the day the nervous tissue adjuvant was injected Previously untreated controls were also included In the animals of group I which had received two prior courses of the saline emulsion of spinal cord symptoms of disease developed in only 12 % whereas in the untreated group 80 % developed nervous system disease Furthermore the degree of paralysis in the rabbits of the pretreated group was minimal whereas in the control animals the disease was severe with clear cut paralysis and encephalitis In addition to the reduction in incidence of paralysis pretreatment provided complete protection from mortality The subcutaneous depot of the homologous antigen injected at the time of spinal cord adjuvant injection was not protective since more than 90 % developed paralysis

Similar protection was afforded by pretreatment provided by prior injections of homologous nervous tissue when heterologous nervous tissue was employed with adjuvant as the encephalitogenic mixture These observations are interpreted as further indirect evidence that the compound involved in production of E A E is organ and not species specific

The protection afforded against the development of E A E could not be passively transferred when serum from immune animals was injected repeatedly by up to a total dose of 70 cc of serum in each rabbit

This method of preventing disseminated encephalitis shares with previously reported techniques a lack of therapeutic value Pretreatment with homologous nervous tissue appears to alter the initial reaction of the host to injection of the disease producing emulsion The mechanism of this protection is not yet understood The possibility that it is due to blocking antibody although not ruled out by these studies is rendered less likely by the failure of passive transfer Other biological phenomena must be considered For example immunological paralysis of the type produced by Felton (81) with pneumococcal polysaccharides might account for the results observed The studies of Johnson et al (82) in adult rabbits Dixon and Maurer (83) in irradiated rabbits Cinader and Dubert (84) and Smith and Bridges (85) with protein antigens in newborn rabbits indicate that this is not a phenomenon peculiar to pneumococcal polysaccharides and mice It would instead appear to have broad biologic expressivity The mechanism operating in this type of immunological paralysis namely failure of antibody formation while antigen remains in the tissues may be comparable to the phenomenon observed when large quantities of nervous tissue are injected repeatedly prior to the production of E A E by nervous tissue with adjuvants It is possible that a similar mechanism accounts for abrogation of tumor immunity by injections of devitalized tissues and prolongation of skin homografts by prior intravenous injections of suspensions of living epidermal cells to the prospective recipients Whatever its mechanism this striking protective effect of prior injections of brain tissue in saline suspension deserves further study

PROTECTIVE EFFECT OF REMOVAL OF THE REGIONAL LYMPH NODE ON THE DEVELOPMENT OF EAE

Preliminary studies revealed that the intradermal injection of the encephalitogenic emulsion was followed within seconds by the appearance of emulsion in the afferent lymphatics and the deposition of the antigenic emulsion in the lymph nodes Serial histological studies of the changes occurring in regional lymph nodes revealed a succession of events deserving further study and analysis The changes already defined include the initial appearance of an antigenic emulsion in the node by direct lymphatic transport within a few minutes after injection into the skin development of an acute cellular inflammatory process proliferation of reticulum cells and development of macrophages development of a striking plasmacytosis intense follicle formation production and release into the lymph and circulation of many basophilic lymphocytes subsequent granuloma and epithelioid cell formation and finally resurgence of acute inflammation and polymorphonuclear infiltration just prior to the development of encephalomyelitis Finally it was found that E A E could be produced in high incidence in rabbits by direct injections of spinal cord adjuvant emulsions into the lymphatic vessels or directly into the popleteal lymph nodes whereas comparable subcutaneous intraperitoneal and intravenous injections of the same material led to a low incidence of the disease

On the basis of these observations together with the finding of Freund and Lipton (77) that removal of the site of injection in the skin did not prevent the development of disseminated encephalomyelitis it was decided that critical information concerning the role of regional lymphatics might be obtained by excision of the regional nodes at varying intervals following an intradermal injection of adjuvant spinal cord emulsion

To our surprise in these experiments excision of the regional nodes 5 minutes 30 minutes 48 hours 5 9 and 12 days after intradermal injection of antigen reduced markedly the incidence of subsequent encephalomyelitis and delayed the time of onset of the disease in those animals in which it did occur We interpret these observations as an indication that the regional lymph node participates directly in the pathogenesis of E A E and indeed plays an essential role in the process in most animals

Further support for this view was obtained in experiments which showed that x irradiation given to the popliteal nodes prior to injection of antigen but not following injection provided similar protection against the development of the disease

ULTRASTRUCTURAL CHANGES IN CENTRAL NERVE FIBERS IN EAE

The pathological picture of E A E has been extensively studied by numerous investigators Essentially the pathologic picture comprises multiple foci of myelin degeneration and perivascular particularly perivenular exudation of inflammatory cells lymphocytes histiocytes and

plasma cells in the central nervous system parenchyma and meninges In this study thin sections of white matter from the central nervous system of guinea pigs developing E A E have been studied to determine the nature of early changes in central nervous system ultrastructure associated with the disease Among the earliest changes observable are those occurring in the mitochondria of the nerve fibers There occur projections of the external limiting membranes disruption and disintegration of cristae followed by vacuolation of the mitochondria This process is associated with a marked increase in the number of mitochondria within the nerve fibers Indeed it is not unusual to find a single nerve fiber on oblique section containing 10 15 mitochondria Following the initial alteration in the outer membrane of the mitochondria clumping and coagulation of neurofibrillae becomes evident These clumps may become adherent either to the inner surface of the myelin sheath or to the abnormal mitochondria It is to be noted that the striking changes in the mitochondria occurred at an early stage while the myelin sheath with its characteristic lamellar ultrastructure remained intact

REACTION OF AUTOGENOUS LYMPHOID TISSUE IN THE BRAIN

Extensive investigations in our laboratory as well as in Kabat s laboratory have shown that in the rabbit guinea pig and monkey E A E may be produced by the parenteral injection of autogenous brain tissue in adjuvants In these experiments the brain tissue was obtained by surgical excision prior to injection These observations have been interpreted to indicate that animals are indeed capable of developing immunological reactions to components of their own tissues It is possible however that the brain components thus injected are not native but altered in some way during preparation of the brain adjuvant mixture To investigate this aspect further autologous lymph nodes were implanted in brains of rabbits through trocars inserted into the brain through the orbit Lymphoid tissue thus implanted survived up to 4 months Both nodular and diffuse lymphatic tissue were present At the center of the implant the nodal reticulum could be recognized as a large open meshwork of pale staining cells Remnants of trabeculæ were also seen Along the pathway to the implant in the brain occurred a typical glial scar without evidence of lymphatic cell accumulation at the periphery of the implant where contact between implant and brain tissue occurred accumulations of plasma cells and macrophages were observed Adjacent to the area of contact an intermediate zone of gliosis neurone destruction and vascularization was present Weigert stains revealed demyelination The latter often extended significantly beyond the zone of puncture into areas of otherwise healthy brain tissue

We interpret these observations to indicate that lymphoid tissue transplants will survive for long periods in the brain Further they represent morphological evidence that implanted lymphoid tissue reacts immunologically against a constituent in brain tissue

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rabbits A high degree of protection against subsequent development of encephalomyelitis was obtained following repeated injections of saline extracts of brain tissue over a four months period This effect could not be attributed to the depot of antigen or desensitization in the classical sense Extensive attempts to demonstrate the existence of a blocking anti body to explain this observation have been unsuccessful

Although prior studies of Lipton and Freund indicate that the site of injection of brain adjuvant emulsion in the skin can be surgically incised without interfering with the development of encephalomyelitis we have demonstrated that removal of the regional lymph node at any time between the injection of the brain adjuvant emulsion and development of encephalitis prevents the development of the disease

Serial studies of the changes occurring in regional lymph nodes reveal a succession of events deserving further study and analysis The changes already defined include the initial appearance of the antigenic emulsion in the node by direct lymphatic transport within a few minutes after injection into the skin development of an acute cellular inflammatory process pro liferation of reticulum cells and macrophages development of striking plasmacytosis intense follicle formation production and release into the lymph and circulation of many basophilic lymphocytes granuloma for mation and finally resurgence of acute inflammation and polymorphonu clear infiltration just prior to the development of disseminated encephalo myelitis Removal of the regional lymph nodes at any of these stages and the consequent interruption of their succession prevents the occurrence of central nervous system disease Furthermore intensive x irradiation applied to the node *prior to* but *not following injection of brain* and adjuvant interrupts the sequence described and prevents the development of encephalomyelitis

Study of the early lesion in the brain and spinal cord reveals perivascular inflammation demyelination and accumulation of mononuclear cells and many plasma cells in all species thus far studied The role of the plasma cell in antibody production indicates that antibody is being formed locally *in the brain during the early phases of this disease*

Employment of the electron microscope to study ultra thin sections showed that among the earliest changes to be observed in the brain and spinal cord in EAE are those occurring in the mitochondria of the nerve processes of myelinated fibers This process appears first to consist of a marked increase in number of mitochondria followed by projections of outer limit ing membranes disruption and disintegration of christae and subsequent vacuolization and swelling of these organelles Although these changes occur while the myelin sheath remains intact they are succeeded by demyeli nization

Finally we have transferred autologous lymph node tissue to the brain where it has survived up to four months The plasmacytic reaction of the surviving lymphoid tissue to the surrounding brain suggests that lumphoid tissue even within the same host may identify the brain tissue as tissue containing a foreign antigen and react to it with allergic inflamma tion

RÉSUMÉ

Bien que l encéphalomyélite diffuse expérimentale ait fait l objet depuis vingt ans d études poussées il reste encore beaucoup a apprendre sur sa nature sa pathogénie et sa relation avec les maladies humaines

La pathologie comparée suggère la ressemblance de cette maladie avec les syndromes post infectieux l encéphalomyélite post vaccinale ou les autres affections inflammatoires et demyelinisantes chez l homme

L encéphalomyélite diffuse expérimentale présente pour la science médicale le fait qu elle est une maladie d un type permettant d etudier par analogie les processus inflammatoires et démyelinisants du système nerveux central et aussi la nature des maladies auto immunisantes en général

L opinion selon laquelle cette maladie expérimentalement provoquée a pour causes des réactions allergiques ou immunologiques est appuyée sur de solides constatations expérimentales

Bien que les preuves manquent encore la plupart des expérimentateurs attribuent une base immunologique a l encéphalomyélite disséminée Le fait que la maladie a été dénommée encephalomyélite allergique expérimentale (E A L) par de nombreux biologistes montre qu il s agit d une opinion répandue

Les donnees dont nous disposons font supposer que l agent encéphalitogene est localisé dans la myéline des tissus du système nerveux central A titre d exemple nous dirons

1° La presence de la substance active dans les tissus du systeme nerveux est certaine elle est spécifique pour l organe mais non pas pour l espece

2° Sa présence dans la matiere blanche a été démontree

3° La myeline ainsi que l activite encéphalitogénique est absente dans le cerveau du fœtus et du nouveau né du lapin

4° L apparition de l activite encephalitogénique est en corrélation directe avec le processus de myelinisation

Des essais faits pour isoler et identifier l agent encephalitogene n ont pas reussi cependant des indications concernant le role de certaines fractions lipo protidiques d une proteine du type collagene presentes dans le cerveau sont tres encourageantes Toutefois a cause du caractere encore discuté et mal défini de la fraction antigenique nous nous sommes servi au cours de toutes nos expériences de moelles epinieres entieres émulsionnées dans de l adjuvant de Freund complet

Dans nos laboratoires aussi bien que pour tous ceux qui les ont experimentes les traitements par salicylates la moutarde a l azote les rayons X et les stéroides surrenaux appliques pour arreter le developpement de l E A E. ont donné des resultats plus ou moins positifs

Bien qu une étude recente d Allen signale les résultats satisfaisants obtenus par des traitements avec des corticoides dans des cas d encephalomyelite apres la rougeole chez l homme une etude accompagnee de doubles tests se recoupant semble cependant désirable

A la suite des observations de Ferrero (et Coll) ayant montre que des injections parenterales prealables de suspensions de tis u cérébral complet

et sans adjuvant atténuent les manifestations de l E A E provoquée chez des cobayes par des injections d émulsions cérébrales dans adjuvant des expériences ont été entreprises dans notre laboratoire sur des lapins mais avec une période d « immunisation » plus longue

Par des injections répétées d extrait salin de tissu cerebral nous avons obtenu un degré de protection élevé a l égard du développement de la maladie Cet effet ne peut etre attribué au depot de l antigene ou à un phénomène classique de desensibilisation Des expériences étendues et poussées ont ete faites sans succes pour expliquer ces observations par la presence d un anticorps bloquant

Bien que de precedentes etudes de Lipton et Freund aient montre que l ablation chirurgicale de la région ou fut pratiquee l injection de la substance cerebrale avec l adjuvant n influe nullement sur l evolution de la maladie nous avons pu démontrer que l ablation des ganglions lymphatiques voisins du lieu d injection pratiquée à n importe quel moment entre l injection de la substance cérébrale avec l adjuvant et l apparition des symptomes d encephalomyélite arretait le développement de la maladie

Nous avons étudie en série les modifications qui se produisent dans les ganglions lymphatiques voisins du lieu d injection ce qui nous a permis de noter une succession de phénomenes méritant d etre étudies et analyses par la suite

Les modifications en question comportent l apparition dans le ganglion par transfert lymphatique direct quelques minutes après l injection sous cutanée de l émulsion antigenique d un processus inflammatoire cellulaire aigu d une proliferation des cellules reticulaires et macrophages de plasmocytose caracteristique d une formation intense de follicules de la formation et de la liberation dans la lymphe de nombreux lymphocytes basophiles de la formation de granulomes et pour finir d une nouvelle poussée inflammatoire aigue avec infiltration polynucléaire Tous ces symptomes font leur apparition immédiatement avant que ne se declare l encéphalomyelite diffuse

L ablation des ganglions pratiquée a l un quelconque de ces stades en interrompt la séquence et empeche l apparition de cette maladie du systeme nerveux central

De plus l irradiation des ganglions par les rayons X interrompt elle aussi la séquence des phenomenes que nous venons de décrire et empeche le développement de la maladie mais seulement dans le cas ou le traitement par rayons X a précede l injection

L examen de lésions recentes du cerveau et de la moelle épiniere a revélé une inflammation perivasculaire une accumulation de cellules mononucleaires et de cellules plasmocytes chez toutes les especes animales étudiees

Le role des plasmocytes dans la formation des anticorps indique qu il y a formation locale d anticorps dans le cerveau pendant les premieres phases de la maladie

Apres l examen au microscope électronique de sections ultra minces nous avons noté que pour l E A E les premieres modifications a apparaitre sont celles qui interessent les mitochondries et le processus nerveux des fibres myelinisées

Ce processus semble tout d abord consister dans une augmentation marquée des mitochondries suivie de la projection des membranes limitantes

externes de l'éclatement et de la désintégration des « christae » ainsi que de la vacuolisation et le gonflement de ces structures Bien qu'au moment où se produisent ces modifications l'enveloppe de la myéline reste intacte elles sont suivies ultérieurement de la démyélinisation

Finalement nous avons transféré dans le cerveau du tissu ganglionnaire lymphatique autologue qui y a survécu jusqu'à quatre mois

La réaction plasmocytaire de ce tissu lymphatique survivant dans le tissu cérébral donne à penser que le tissu lymphatique même chez le même hôte peut reconnaître dans le tissu cérébral un antigène étranger auquel il réagit sous la forme d'« inflammation allergique »

ZUSAMMENFASSUNG

Obwohl in den letzten 20 Jahren die experimentelle disseminierte Encephalomyelitis weitgehend erforscht wurde blieb doch vieles bezüglich ihrer Natur Pathogenese und Beziehung zur menschlichen Erkrankung zu klären. Die vergleichende Pathologie vermutet eine Ähnlichkeit zwischen dieser experimentellen Erkrankung und der nach Infektionen oder nach einer Vaccination auftretenden Encephalomyelitis und gewissen anderen demyelinisierenden und entzündlichen Erkrankungen des Menschen Der Wert einer experimentellen disseminierten Encephalomyelitis für die medizinische Forschung liegt in ihrer Brauchbarkeit als Modell zum Studium von demyelinisierenden und entzündlichen Prozessen im Zentralnervensystem sowie auch als Modell die Natur von auto immunen Erkrankungen im allgemeinen zu studieren

Die gewonnenen Daten stützen die Ansicht dass für die Entwicklung dieser experimentellen Erkrankung eine immunologische Antwortreaktion oder allergische Reaktion verantwortlich sei Obgleich ein gültiger Beweis noch nicht erbracht ist, scheint den meisten Untersuchern als beste Arbeitshypothese dass die experimentelle disseminierte Encephalomyelitis eine immunologische Basis hat Dass diese Ansicht weit verbreitet ist spiegelt sich in der Tatsache wieder dass diese Erkrankung von vielen Untersuchern als experimentelle allergische Encephalomyelitis (EAE) benannt wurde [illegible]

[illegible]

ist organ— aber nicht artspezifisch

2° Die Lokalisation innerhalb der weissen Hirnsubstanz konnte gezeigt werden

3° Beide Myelin und encephalitiserzeugende Fähigkeit sind nur mangelhaft im Hirn des fetalen oder neugeborenen Kaninchen vorhanden

4° Das Auftreten der encephalitiserzeugenden Fähigkeit steht in deutlicher Wechselbeziehung mit dem Myelinisierungsprozess

Versuche dieses encephalitiserzeugende Agens zu isolieren und identifizieren waren erfolglos obwohl die Studien ermutigten gewisse proteolipide Fraktionen und ein collagen ähnliches Protein im Gehirn damit in Zusammenhang zu bringen Wegen der Gegensätze und Verwirrung bezüglich der Antigenfraktionen entschlossen wir uns jedoch, in all unseren

Experimenten ganzes im kompleten Adjuvans ein nach Freund emulgiertes Ruckenmark als Antigen zu verwenden

Versuche das Auftreten einer EAE durch Behandlung mit Salicylaten N Lost Rontgenbestrahlung und Nebennierensteroiden zu verhuten sind mehr oder minder erfolgreich in unserem und in anderen Laboratorium angestellt worden. Obgleich Allen in einer neuen Arbeit vermutet dass eine Behandlung einer beim Menschen nach Masern auftretenden Encephalo myelitis mit Nebennierensteroiden von signifikantem Erfolg sei scheint doch Kontrolle im doppelten Blindversuch angezeigt

Die Beobachtungen von Ferraro et al dass vorhergehende parenterale Injektionen einer Hirngeweb suspension ohne das komplette immunolo gische Adjuvans bei Meerschweinchen die Erkrankungsmoglichkeit an Encephalomyelitis bei folgenden Injektionen von Gehirn Adjuvans Emul sionen herabsetzten regten eine Versuchsreihe in unserem Laboratorium an in der wir eine etwas langere Immunisierungsperiode bei Kaninchen verwendeten Nachuber eine Periode von 4 Monaten wiederholt verabreich ten Injektionen von Salzextrakten aus Hirngewebe erzielten wir hochgra digen Schutz gegen ein spateres Auftreten einer Encephalomyelitis Dieser Effekt konnte weder dem Antigendepot noch einer Desensibilisierung im klassischen Sinne zugeschrieben werden Ausgedehnte Versuche die Existenz eines blockierenden Antikorpers zur Erklarung dieser Beobachtung nachzuweisen waren erfolglos

Obwohl fruhere Studien von Lipton und Freund zeigen dass die Injek tionsstelle einer Gehirn Adjuvans Emulsion in der Haut chirurgisch inzisiert werden kann ohne storend auf die Entwicklung einer Encephalo myelitis einzuwirken konnten wir nachweisen dass die Entfernung der regionaren Lymphknoten zu jeder Zeit zwischen der Injektion einer Gehirn Adjuvans Emulsion und dem Auftreten der Encephalitis die Entwicklung dieser Erkrankung verhindern kann

Reihenuntersuchungen der in den regionaren Lymphknoten auftretenden Veranderungen zeitigten eine Serie von Erscheinungen die weiteres Studium und Analyse verdienen Die genau bestimmten Veranderungen ergeben das initiale Erscheinen der auf den Lymphwege herantransportierten Antigen Emulsion im Lymphknoten schon einige Minuten nach der Injektion in die Haut sowie das Auftreten eines zellularen akutentzundlichen Prozesses die Proliferation von Retikulumzellen und Makrophagen das Auftreten einer auffallenden Plasmacytose und intensive Follikelbildung die Bildung und Abgabe an den Lymphstrom und Zirkulation von vielen basophilen Lymphozyten Granulombildung und zuletzt das Auftreten einer akuten Entzundung und polymorphonuklearen Infiltration gerade vor der Bildung einer disseminierten Encephalomyelitis Die Entfernung der regionaren Lymphknoten in jedem dieser Stadien und folgende Unterbrechung ihrer nachkommenden Reihe verhindern das Erscheinen einer Erkrankung des zentralnervosen Systems Weiterhin unterbricht intensive Rontgenbes trahlung des Lymphknotens vor der — nicht aber danach — Gehirn Adju vans Injektion die beschriebene Reihenfolge und verhutet das Auftreten einer Encephalomyelitis

Studien einer fruhen Lasion im Gehirn und Ruckenmark zeigten peri vaskulare Inflammation Demyelinisierung und Anhaufung von mononu klearen Zellen

Die Rolle der Plasmazelle im Rahnem der Antikorper Produktion lasst vermuten dass Antikörper lokal im Hirn wahrend der ersten Phasen dieser Erkrankung gebildet werden

Bei Verwendung des Elektronenmikroskopes zum Studium ultradunner Schnitte konnte gezeigt werden dass unter den ersten Veranderungen, die bei EAE im Hirn und Rückenmark beobachtet werden konnen solche in den Mitochondrien der Nervenfortsatze myelinisierter Fasern sind Dieser Fortsatz scheint zuerst an Zahl bemerkenswert zugenommene *Mitochondrien zu enthalten* gefolgt von einem *Aufwerfen der nach aussen* abgrenzenden Membranen Zerreissen, Disintegration und nachfolgend Vakuolisierung und Anschwellen dieser Organellen Obschon diese Veranderungen erscheinen wahrend die Myelinscheiden noch intakt bleiben, sind *sie doch von einer Demyelinisierung gefolgt*

Schliesslich und endlich haben wir autologes Lymphknotengewebe in das Gehirn übertragen wo es bis zu 4 Monaten uberlebte Die gegen das umliegende Gehirn gerichtete plasmazytische Reaktion des uberlebenden *lymphoiden Gewebes lasst vermuten dass lymphoides* Gewebe innerhalb des gleichen Wirtes Gehirngewebe als Fremdantigen enthaltendes Gewebe identifizieren und dagegen mit einer allergischen Inflammation reagieren kann

RESUMEN

Aunque la encefalomielitis diseminada experimental ha sido muy estu*diada en los ultimos 20 años* queda *mucho por averiguar sobre* su naturaleza, patogénesis y relación con la enfermedad en el hombre El valor de su estudio reside en su utilidad como modelo de procesos desmielinizantes e inflamatorios del sistema nervioso central y de enfermedad de autoinmunidad [illegible] ...perimental es conse[illegible] ...ta sostenido [illegible] ...falomielitis alérgica experimental (EAL) con que ha sido designada

El agente causal parece estar contenido en la mielina de los tejidos nerviosos centrales Asi por ejemplo

1º El material activo presenta especificidad de órgano, pero no de especie

2º Se ha demostrado su localizacion en la sustancia blanca

3º Está ausente en el cerebro del feto o del conejo *recién nacido*

4º La actividad corre parelela con el proceso de mielinización

Los intentos de aislar e identificar al agente productor de la encefalomielitis han fracasado hasta la fecha, aunque algunos estudios sobre ciertas fracciones de proteolípidos y de sustancias colágenas *son prometedores* Debido a la confusión y controversia existentes a este respecto en todos los ensayos los autores han utilizado médula entera emulsionada con los adyuvantes de Freund

Los ensayos *para impedir* el desarrollo de la EAE mediante *el uso de* salicilatos, rayos X y esteroides adrenales han dado resultados *más o menos* favorables al igual que en manos de otros investigadores

Las observaciones de Ferraro et al en el sentido de que inyecciones por

vía parenteral de tejido cerebral sin adyuvantes disminuyen la incidencia de encefalomielitis provocadas por extractos de cerebro más adyuvantes han sido confirmadas utilizando tiempos de inmunización más prolongados (cuatro meses) y en conejos en lugar de cobayos Este efecto no puede ser explicado por depósito de antígeno ni por una desensibilización en el sentido clásico y tampoco se ha podido demostrar la presencia de un anticuerpo bloqueante

A pesar de los estudios de Lipton y Freund quienes encontraron que el desarrollo de la encefalomielitis no es modificado si se aísla quirurgicamente el sitio de la inyección de antígeno más adyuvante los autores han encontrado que la eliminación de los ganglios linfáticos regionales correspondientes impide la evolución de la enfermedad Las modificaciones que aparecen en estos ganglios incluyen la aparición de la mezcla inyectada por transporte linfático pocos minutos después de la inyección la aparicion de un proceso inflamatorio agudo la proliferacion de células reticuloendoteliales y de macrófagos intenso desarrollo folicular producción y liberacion en la linfa de linfocitos basófilos formación de granuloma y finalmente inflamación aguda e infiltración polimorfonuclear inmediatamente antes de la encefalomielitis La extirpación de los ganglios en cualquiera de estas fases interrumpe el proceso y ademas lo mismo puede obtenerse por irradiación con rayos X antes pero no despues de la inyección de antígeno

El estudio de la lesión producida revela una inflamacion perivascular desmielinización y acumulación de células mononucleares y plasmáticas en todas las especies hasta ahora estudiadas El papel de las celulas plasmáticas en la producción de anticuerpos indica que el anticuerpo se forma localmente en el cerebro durante la primera fase de la enfermedad

El uso del microscopio electronico demuestra que entre las primeras modificaciones observadas en el cerebro y la medula en la EAE están aquellas que tienen lugar en el mitocondrio que se verifican inmediatamente antes de la desmielinización

Los autores se refieren finalmente al transplante de ganglios al cerebro con supervivencia de hasta cuatro meses y a las reacciones observadas en tal caso que sugieren que el tejido linfoide aun del mismo individuo identifica en el cerebro un antígeno extraño ante el cual reacciona con una «inflamacion alergica»

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DIE BEDEUTUNG DER GEWEBS ANTIKÖRPERBILDUNG FÜR DIE PATHOGENESE UND KLINIK ENTZÜNDLICHER NIERENERKRANKUNGEN

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EXPERIMENTELLE ERGEBNISSE

Seit den grundlegenden Versuchen von Masugi (8) ist bekannt daß heterologe Organ Antiseren im Empfangerorganismus eine entzundliche Gewebsreaktion desjenigen Organgewebes auszulösen vermogen gegen das der injizierte Organantikorper gerichtet ist — Im Speziellen entsteht eine experimentelle den Verhältnissen beim Menschen angeglichene Nierenentzundung dann wenn das sogenannte Nephrotoxin das ist der nephrotrope Organ Antikorper mit den Nieren auch des Empfangertieres in Reaktion tritt Pearce (10) fand daß zur Erzeugung eines heterologen nephrotropen Serums die *Nierenrinde* als Antigen genugt daß dem Mark also keine spezifische serologische Funktion zukomme Später haben Krakower und Greenspoon (4) zu zeigen vermocht daß das Nierenantigen an den Basalmenbranen der Glomeruli lokalisiert sein muß — Die biochemische Struktur dieses Antigens ist bis heute jedoch nicht aufgeklärt (siehe bei Sarre) (15) Entsprechend werden die heterologen nephrotropen Antikörper am Gefäßapparat der Glomeruli nicht etwa an den Parenchymzellen gebunden (Pressman und Sherman) (12) wie sich vor allem aus Isotopenmarkierungen dieser Gewebsantikörper ergeben hat Diese Bindung erfolgt außerordentlich schnell die einmalige Bindung genugt um eine Glomerulonephritis zu erzeugen

Untersuchungen uber Wesen und Wirkung heterologer Organ Antikorper bleiben selbstverstandlich dem Experiment vorbehalten und sind unter klinischen Bedingungen nicht vorstellbar — Es ergibt sich aber die folgerichtige Frage ob nicht doch auch unter klinischen Bedingungen eine Organ Antikörperbildung möglich werden könnte die dann allerdings gegen das *eigene* Organ gerichtet sein müßte also einem homologen Organ Autoantikorper entsprechen wurde

Experimentelle Versuche schliessen diese Moglichkeit nicht aus In der variierten Technik nach Freund gelingt es unter Zuhilfenahme von Adju



Abb. 1. — a) Kolonieartige Tuberkelbakterienansammlungen in de Kapillarschlingen eines Glomerulus mit beginnenden entzündlichen Veränderungen.
Karbol-Fuchsin — Häm. — Färbung.
Abb.-Masstab 1200 : 1.

b) Ausschnittvergrösserung von 2a. Die dunkeln Massen entsprechen Tuberkelbakterien.
Abb.-Masstab 4500 : 1.

vantien unter denen abgetötete Streptokokken oder tote Tuberkelbakterien dominieren auch gegen homologes Organgewebe zu sensibilisieren Ein derart z B bei Ratten erzeugter Iso Antikörper gegen Niere erwies sich als ebenfalls gegen die Nieren*rinde* nicht gegen Markanteile des Organs



ABB . — Rindenknötchen mit mehreren eingeschlossenen Glomeruli (Häm — Eosin — Färbung Abbmasstab 180 1)

gerichtet und daher auch spezifisch absorbierbar (Vorlaender) (18) Interessanterweise ist bis zum heutigen Tage aber nicht bewiesen worden daß auch die Bindung dieses homologen Gewebsantikörpers zu irgendwelchen *Entzündungserscheinungen im Erfolgsorgan zu führen vermochte* Diesbezügliche Folgerungen von Cavelti der in einer homologen Nieren antikörperbildung die eigentliche Ursache selbst der menschlichen Glomerulonephritis zu beweisen suchte waren in Nachuntersuchungen (Bohle und Mitarb (1) Vorlaender) (18) nicht zu bestätigen Trotz völlig gleichartiger Wirkungsrichtung sind heterologe und homologe Organ Antikörper demnach voneinander unterschieden dadurch daß der heterologe Organ Antikörper zugleich gegen artfremdes Eiweiß gerichtet ist der homologe nicht — Dennoch kommt auch der homologen Organ Antikörperbildung pathogenetische Bedeutung zu Sie wird deutlich in der Beeinflussung eines zusätzlichen Infektgeschehens z B erkranken Ratten *selbst bei künstlicher Infektion mit abnorm hohen Bakterien Dosen sehr* selten an Tuberkulose Kommt es aber zum Haften des Infektes dann

bleiben die Nieren so gut wie immer frei, obwohl spezifische Herdbildungen in anderen Körperorganen (Leber, Lunge) vorhanden sind. Die natürliche Resistenz der Rattenniere gegenüber der Tuberkuloseinfektion kann nun gleichsam durchbrochen werden, wenn die Tiere gleichzeitig mit einer künstlichen intraperitonealen Tuberkuloseinfektion eine einmalige ausreichende Dosis eines homologen Nierenantikörpers erhalten. Die Folge ist eine statistisch einwandfrei gesicherte Häufung von Ratten-Nierentuberkulose (Fig. n° 1), wobei die Herdbildungen nahezu ausschließlich wieder [illegible] Man gewinnt den [illegible] if die Nierenrinde [illegible] ind K. O. Vorlaen[illegible]

KLINISCH SEROLOGISCHE ERGEBNISSE

Zahlreiche Untersucher der letzten Jahre (Schwentker und Comploier, Pfeiffer und Brüch (11), Sarre und Rother (15), Rejholec (14), Vorlaender (18), in allerjüngster Zeit C. Gajdusek (3)) stimmen darin überein, daß auch unter *klinischen* Bedingungen überwiegend im Verlauf der diffusen Glomerulonephritis Serumveränderungen auftreten, die nicht einer Antikörperbildung gegen bakterielle Antigene entsprechen, sondern gegen Rezeptoren des Gewebes gerichtet sein müssen. Zu ihrem Nachweis stehen verschiedene Verfahren zur Verfügung: Die modifizierte Complementbindung, di[e] Agglutination mit Gewebsextrakten beladener Collodiumpartikel, eine Variation der von Grabar erdachten und von Boyden für Tuberkuloseprobleme erprobten passiven Haemagglutination, neuerdings auch mit Latexträgern durchgeführt, schließlich der aus dem Coombstest abgeleitete Antihumanglobulinconsumptionstest (Steffen) (17). Jede dieser Methoden hat eine gewisse Fehlerbreite, gegen jede gibt es kritische Einwände, die jedoch vor allem für die neuerdings wieder modifizierte Co[mplement]bindungsreaktion (Gajdusek) (3) und für die passive Haemagglutination weitestgehend entkräftet sind.

Trotz der Verschiedenartigkeit der technischen Durchführung sind nahezu sämtliche Untersucher übereinstimmend zu folgendem Ergebnis gelangt:

Der positive serologische Befund erweist sich auf die Gruppe derjenigen Nierenerkrankungen beschränkt, die mit entzündlichen Veränderungen im Bereich der Glomeruli einhergehen; das sind vor allem die verschiedenen Stadien der diffusen haematogenen Glomerulonephritis, weiter die Herdnephritis und schließlich die entzündliche Nierenbeteiligung beim Erythematodes, deren Sonderstellung durch besondere pathologisch-anatomische Merkmale bedingt wird.

Der positive serologische Befund ist weiterhin vorwiegend jenen Nephritisformen zugeordnet, die zur chronischen Progredienz und Übergang in Schrumpfniere neigen (Stadium II und III nach Volhard). *Er fehlt weitestgehend der akuten Glomerulonephritis wie dem prognostisch gutartigen Stadium I der chronischen Formen ohne Tendenz zur stetigen entzündlichen Fortentwicklung.*

Das verantwortliche Antigen ist freilich auch hier bisher unbekannt; drei Möglichkeiten stehen zur Diskussion:

1 Es kann sich um eine Verbindung von Streptokokkenanteilen mit Nierenenweiß handeln In d r Tat haben Streptokokken der Gruppe A (Lancefield) wie sie fur die Auslosung einer Nieren entzundung uberwiegend bedeutungsvoll sind eine besondere Tendenz sich mit Complex verbindungen von Eiweissen mit Polysaccharidanteilen zu verbinden auch ist bekannt daß homologe Organ antikorperbildungen gegen Niere nahezu ausschließlich dann auftreten wenn Streptokokkeninfekte vorausgingen nicht andersartige bakterielle Einflusse (Sarre und Rother) (15)

2 Es steht zur Diskussion inwieweit durch d n Vorgang d r Entzundung Stoffe in Freih it gesetzt werd n die unter phy iologischen Bedingungen nicht in den Kreislauf gelangen und daher als korperfremd also antigen wirksam *empfunden werd n Man denkt vor allem an Renin ein Ferment* das ja unter den Bedingungen d r Entzundung erst in Freiheit gesetzt und in der Folge fur die nephrogene Hypertonie verantwortlich wird Doch konnte ein exakter Beweis fur die spezifische Antigennatur des Renins bis heute nicht erbracht werden wenn auch Überempfindlichkeitserscheinungen gegenuber Renin haltigen Nierenextrakten im Hauttest gerade bei *Nephritikern gefund n wurden (Moeller) (9)*

3 Es steht weiter zur Diskussion d ß durch die Entzundung im Bereich d r Glomeruli Stoffe des Gewebes so abgewandelt werden daß sie als körperfremd empfunden und damit immunisatorisch wirksam werden diese Gewebsantikörper werden jedoch auch an Extrakte aus normalem Gewebe gebunden sie mußten demnach uber determinierende chemische Gruppen verfugen *die auch in normalen Geweben vorkommen (vergleiche* die parallelen Vorstellungen zum Zustandekommen der Sensibilisierung gegen Gamma Globulin bei rheumatischen Erkrankungen)

Wenn die Natur des verantwortlichen Nierenantigens z Zt auch noch nicht voll aufgeklart ist — nur die Lokalisation in der Nierenrinde ist *gesichert! — darf es demgegenuber vor allem auf Grund der neuerdings von* Gajdusek (3) vorgelegten Befunde heute doch als uberwiegend wahrscheinlich angenommen werden daß die serologisch erfaßbaren Veranderungen einer echten Antikörperbildung entsprechen die man mit Recht als Organ Auto Antikörper Bildung zu bezeichnen hat

FOLGERUNGEN FÜR PATHOGENESE UND KLINIK

Es ist bis heute niemals bewiesen worden daß eine Organ Autoantikorper *Bildung gegen Niere zur eigentlichen Ursache einer akuten haemato*genen Glomerulonephritis zu werden vermochte so sehr man auch an eine solche Moglichkeit gedacht haben mag (Cavelti) (2) Lange und Mitarb (5)

Eine akute Glomerulonephritis entsteht vielmehr in der uberwiegenden Mehrzahl der Falle etwa in 1 3 Wochen nach einem Streptokokkeninfekt und *zu einer Zeit wo die Bakterien selbst am Eintrittsort nicht mehr* nachzuweisen sind das Organ bleibt durchweg steril — Erst die immunologische Auseinandersetzung mit diesem Infekt nachweisbar durch abnorm hohe Antikorper Befunde gegen die verschiedenen Streptokokken Antigene kann demnach zur Ursache der akuten Nephritis werden wobei die Glomeruli *der Nierenrinde der hauptsachliche Sitz dieser Antigen Antikörper* Reaktion sein mussen Selbst die neuerdings im amerikanischen Schrifttum

so viel diskutierte Streptokokkus Typ 12-Nephritis folgt diesem Mechanismus. In eigenen Untersuchungen ließ sich nachweisen, daß eine Streuung dieser Bakterien in die Nieren die Entstehung einer interstitiellen Nephritis zur Folge hat; eine dem Menschen vergleichbare Glomerulonephritis entsteht demgegenüber nur durch künstliche Sensibilisierung gegen diesen speziellen Streptokokken-Typ, also ebenfalls als Folge einer immunologischen Auseinandersetzung. Die besondere nephritogene Wirkung dieser Erreger ist bedingt durch ein besonders gutes Haften an den Glomeruli mit nachfolgender Antigen-Antikörper-Reaktion.

Dem in den meisten Fällen also hyperergischen Mechanismus der Nephritisentstehung folgt die oben beschriebene Organ-Antikörperbildung erst als Zweitvorgang nach; irgendwelche Konsequenzen für die Pathogenese, die mit diesem immunisatorischen Sekundärgeschehen zusammenhängen, können demnach niemals die Krankheitsursache, sondern lediglich die weitere Entwicklung zur Chronizität oder zum Rezidiv der Entzündung betreffen; wie schon gesagt, erweist sich die Gewebs-Antikörperbildung ja auch serologisch den klinisch rezidivierend oder progredient verlaufenden Nephritisformen ganz überwiegend zugehörig.

Jeder Kliniker kennt diesen schubweisen Übergang zur Chronizität und weiß, daß diese Schübe vielfach durch Streuungen aus einem bakteriellen Herd oder durch neue, oft banale interkurrent erworbene Infekte ausgelöst werden. Sollte man nicht auch unter klinischen Bedingungen in Erwägung ziehen, daß die Gewebs-Auto-Antikörperbildung für die Steuerung dieser Infekte bzw. der einzelnen bakteriellen Antigene auf die Niere und für ihr verbessertes Haften an den Glomeruli verantwortlich sein könnte, wie das für das Modellbeispiel der Nierentuberkulose der Ratte bewiesen wurde? Diese Theorie ist einfach und neuartig, umgeht die schwer verständliche These von der Unterbrechung des „horror autotoxicus" von Ehrlich und fügt sich folgerichtig in die klinischen Gegebenheiten ein. Freilich bleibt der letzte Beweis an die volle Aufklärung des Nierenantigens gebunden.

Klinische wie serologische Beobachtungen bei Jugendlichen sind geeignet, die Bedeutung der beiden hier für die Nephritisgenese und -Entwicklung zur Diskussion gestellten immunologischen Vorgänge zu stützen. Die Erfahrung besagt, daß die ersten Lebensjahre von der typischen haematogenen Glomerulonephritis in der Regel verschont bleiben. Gerade in diesen Jahren aber besteht auch eine gegenüber dem Erwachsenen erheblich verminderte immunologische Reaktionsbereitschaft. Erst im Vorschulalter treten echte diffuse Glomerulonephritiden auf; hier häufig nach Scharlach (Linneweh) (7) klinisch dominieren dabei die akut verlaufenden, aber nicht zur Progredienz neigenden Formen; serologisch ist diese Altersphase gekennzeichnet durch ein starkes, doch rasch sich erschöpfendes Antikörperbildungsvermögen. Chronisch progrediente Nierenentzündungen bleiben demgegenüber den späteren Lebensjahren vorbehalten. Erst zu dieser Zeit liegt aber auch die voll ausgebildete, zur Synthese differenter Antikörper befähigte immunologische Reaktionsbereitschaft vor; erst jetzt scheint die Synthese von Auto-Antikörpern ermöglicht zu werden.

Letterer (6) hat wiederholt davor gewarnt, einem Einzelvorgang zu ausschließliche Bedeutung für die Pathogenese einer Erkrankung zuzumessen; häufig genug bildet erst das Zusammentreffen mehrerer Faktoren die Grundlage für die Entwicklung des krankhaften Geschehens.

wie der sog Amyloidniere Die klinische Sonderstellung des *Erythematodes* erfahrt ihre Pragung durch das L E Phaenomen das in uber 80 % aller Falle nachweisbar wird ursachlich ist eine Auto Antikörperbildung gegen Nucleoproteide des Zellkerns von Leukozyten verantwortlich unabhängig davon kommen Auto Antikorperbildungen gegen plasmatische

Entzundung der Gefäße vor allem der Nierengefaße in den Vordergrund nun wiederum begleitet und vielleicht auch mitverursacht durch Gewebs Auto-Antikörper von unterschiedlicher Spezifitat kaum irgendwo sonst

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Man war lange Zeit geneigt auch die Ablagerung von Amyloid wie sie in den Nieren zum Bild der sog *Amyloid Niere* fuhrt als Folge einer Auto praecipitation zwischen abgebautem daher antigenwirksamem Organeiweiß und einem spezifisch gerichteten Auto Antikorper von Globulinnatur zu erklären wobei dieser Vorgang primar wiederum durch die chronische Infektion eingeleitet wird (Letterer) (6) Man mißt diesem Auto Immunitats phaenomen dessen Existenz im Übrigen durch fluorescenz optische Ver fahren gesichert werden konnte heute jedoch nicht mehr die gleiche Bedeutung bei Vielmehr mussen nach Letterer mehrere verschiedenartige humorale Bedingungen erfullt sein damit es zur Amyloidablagerung kommt doch genugt auch das allein nicht es ist zusatzlich ein gewebliches Prinzip notwendig und erst das Zusammentreffen aller dieser Faktoren bildet die pathogenetische Grundlage der Amyloidose

FOLGERUNGEN FUR DIE KLINISCHE DIAGNOSTIK UND PROGNOSE

gegen Niere gerichteter homologer Gewebs Antikorper Gamma Globulin Vermehrung und BKS Beschleunigung charakterisieren das Bild der sub chronischen zur Progredienz neigenden Glomerulonephritis kommt ein positiver Nachweis von C reaktivem Protein hinzu (es handelt sich um ein im Verlauf der Entzundung entstehendes Paraprotein ohne Antikorper Charakter) so ist damit ein weiterer empfindlicher wenn auch nicht krankheitsspezifischer Gradmesser der im Gewebe fortschreitenden Ent

zundung gegeben Akute Glomerulonephritisformen mit guter Prognose zeigen die gleiche serologische Konstellation doch ohne Gewebsantikörper — Der zusätzliche Nachweis d s I F Faktors würd beweisend sein fur das Vorhandensein einer chronisch entzundlichen Erythematodes Nephritis

Globulin Test würde beweisen daß die Niere im Rahmen einer rheumatischen Grunderkrankung entzündlich mitbeteiligt ist — Positiver Gewebs Antikörper Nachweis gegen Nierenrinde beweist immer die entzundliche Beteiligung der Glomeruli und schließt eine interstitielle Nephritis oder Nephrosklerose aus — Fortbestand erhöhter Anti o Streptolysine uber lange Zeiträume nach akuter Nephritis ist prognostisch ebenso ernst zu bewerten wie der constant positive Gewebs Antikörper Befund

FOLGERUNGEN FUR DIE KLINISCHE THERAPIE

Es ist bis heute niemals gelungen eine Glomerulonephritis mit Antihistaminsubstanzen erfolgreich zu behandeln auch Cortison bleibt vor allem bei chronischen Fällen ohne sicheren Erfolg verschlimmert häufig sogar durch zusätzliche Wasserretention Aussicht auf Erfolg kann nur ein Mittel haben das geeignet ist in die fur Entwicklung und Chronizität einer Glomerulonephritis verantwortlichen immunbiologischen Vorgänge einzugreifen Immerhin hat man sich diesem Problem jetzt auch von pharmakologischer Seite zugewandt

Die nächstliegende Folgerung fur die klinische Therapie betrifft vor allem die Vermeidung schädlicher Eingriffe Welchem Kliniker ware die akute Anurie bei subchronischer oder chronischer Nephritis als Folge einer wenn auch gruppengleichen Bluttransfusion unbekannt sie war uns besonders eindrucksvoll bei der Erythematodes Nephritis Interessanterweise werden Transfusionen umso besser verträglich je ausgesprochener sich eine Uraemie oder je ausgesprochener sich eine Dysproteinaemie mit Neigung zu nephrotischem Einschlag entwickeln Hier treten sowohl die bakteriell Sensibilisierung als auch die Gewebs Antikörper Bildung meßbar zuruck ... D... weitgehende Kontrain... terologer ... sich bei ... taemie im ... Verlauf der Nierenentzundung durch parenterale Eiweißinfusionen auszugleichen sind nur gerechtfertigt mit gereinigten nicht antigenwirksamen Serumfraktionen (z B Humanalbumin) und erfordern auch dann noch erhebliche Vorsicht In allen diesen Fallen hat man sich vorzustellen daß das immunbiologische Geschehen in der Nierenrinde erneut aktiviert wird — Schließlich erwies sich auch das Schicksal von Nierenhomotransplantationen aus therapeutischer Indikation als mit der Frage der spezifischen ... verknupft wahrscheinlich liegt in der Auto... dennoch individuell verschiedene ...ache des Transplantatunterganges ... begrundet

ZUSAMMENFASSUNG

Das für die Entstehung der Masugi nephritis also für die Bildung und Bindung des Nephrotoxins verantwortliche Gewebs Antigen der Niere ist in der Rinde nämlich im Bereich der Basalmembranen der Glomeruli gelegen. In der Technik nach Freund gelingt es auch im homologen Milieu gegen Niere zu sensibilisieren die Lokalisation des Gewebsantigens ist die gleiche die correspondierenden Gewebs (Iso bzw Auto) Ak bewirken jedoch *keine* der heterologen Nephrotoxin Wirkung vergleichbare Nierenentzündung. Doch lässt sich beweisen dass bakterielle Infekte selbst bei grösster Organresistenz (Rattenniere[1]) durch Vorbehandlung mit homologen Organ antiserum bevorzugt in der Nierenrinde zum Haften und zur Entwicklung gebracht werden können. Selbst unter klinischen Bedingungen aber ausschliesslich als Folge einer durch bakterielle Frem dantigene Einwirkung bereits ausgelösten Glomerulonephritis treten Serum veränderungen auf die nicht einer Ak bildung gegen die Nierenrinde gerichtet sind. Die chemische Natur dieser Gewebsantigene ist unbekannt doch ist sicher dass erst die Entzündung zum Auftreten antigen wirksamer Stoffe im Bereich der Nierenrinde führen kann.

Dieser immunologische *Sekundärvorgang* bleibt den progredienten Krankheitsformen zugeordnet und gewinnt damit erhebliche Bedeutung für die Krankheitsentwicklung klinische Diagnose und Prognose. Kinder bleiben bis zum Schulalter von der Entwicklung dieses Zeitvorganges verschont, entsprechend ist der Übergang zur Chronizität im Vorschulalter eine grosse Seltenheit.

Dennoch wäre es ein Fehler die Probleme der chronischentzündlichen Nierenerkrankungen zu aus schliesslich unter dem Blickwinkel der Gewebs auto Sensibilisierung zu betrachten nicht zuletzt das Beispiel der Nieren entzündung beim Erythematodes und das Beispiel der Amyloid Niere beweisen die grosse Bedeutung nicht nur humoraler sondern auch gewe blicher Faktoren erst das Zusammentreffen mehrerer Faktoren bestimmt die pathogenetische und klinische Entwicklung.

RÉSUMÉ

L'antigène tissulaire du rein responsable de la nephrite de Masugi c'est à dire de la formation et de la fixation de nephrotoxine se localise dans le cortex rénal au niveau des membranes basales des glomérules.

Par la technique de Freund on parvient à obtenir une sensibilisation contre le rein meme dans un milieu homologue dans ce cas la localisation de l'antigene tissulaire reste la meme mais les anticorps tissulaires corres pondants (iso ou auto anticorps) ne causent pas d'inflammation du rein comparable à celle que provoque la nephrotoxine hetérologue.

On peut cependant démontrer que les effets des toxines bactériennes meme dans les cas ou il existe une resistance spontanée élevée de l'organe (rein de rats) peuvent par un traitement prealable d'anti serum de l'organe se manifester et se localiser plus particulierement dans le cortex rénal.

De meme dans

glomerulonéphrite déjà déclenchée se produisent des modifications sériques qui ne reflètent pas la formation d anticorps anti bactériens mais qui révèlent la *présence d anticorps contre le cortex rénal*

On ne connaît pas la nature chimique de ces antigènes tissulaires mais il est établi que seule l inflammation rénale provoque l apparition de substances antigéniques actives dans le cortex rénal

Ce *processus immunologique secondaire ne se rencontre* que dans les formes évolutives et progressives ce qui lui confère une grande importance pour le développement de la maladie et pour le diagnostic et le pronostic cliniques

Ce processus secondaire épargne les enfants jusqu à l âge scolaire et de ce fait l évolution vers une maladie chronique est d une exceptionnelle rareté chez les enfants n ayant pas atteint cet âge

Cependant ce serait une erreur de ne considérer les néphrites chroniques que sous le seul angle d une auto sensibilisation des tissus l inflammation rénale dans les états érythématoides et dans l amylose rénale prouvent la grande importance des facteurs non seulement humoraux mais aussi tissulaires seule la coincidence de plusieurs de ces facteurs peut determiner le sens du développement clinique et pathologique de la maladie

SUMMARY

The kidney tissue antigen, responsible for the Masugi type nephritis i e the production and the fixation of nephrotoxins, is localized in the renal cortex and particularly in the glomerular basal membrane

Using Freund s technique it is possible to obtain sensitization to kidney *even in homologous conditions the localization of the* tissue antigen is in these cases identical but the corresponding antibody (iso or auto anti body) does not produce an inflammation of the kidney comparable to that caused by the heterologous nephrotoxin

It is nevertheless possible to prove that the bacterial toxins even in the instances where a high spontaneous resistance of the organ exists (rat kidney) can affect and produce lesions of the renal cortex if the organ antiserum is previously administered to the animal

Similarly there is evidence in clinical conditions but only after the establishment of a glomerulo nephritis of humoral changes which do not indicate the production of an anti bacterial antibody but rather the presence of an antibody against renal cortex

The chemical nature of the tissue antigens remains still to be proved but it is *well established that only the kidney inflammation determines* the appearance of antigenic substances active on the renal cortex This secondary immunological process is only observed in the progressive evolution forms of glomerulonephritis and this is of a great importance for the evolution of the disease as well as for its clinical diagnosis and prognosis

This secondary process respects usually children until school age and consequently the evolution of the disease towards chronic state is of exceptional rarity in young children

However it would be an error to consider chronic nephritis only from the view-point of tissue autosensitisation the inflammation of the kidney

in the erythematoid states and in renal amyloŝis proves the great importance of not only the humoral but also the tissue factors Only the coincidence of several of those factors may determine the clinical and pathological development of the disease

RESUMEN

El antígeno tisular del riñón responsable de la nefritis de Masugi es decir de la formación y fijación de nefrotoxina se localiza en las membranas basales de los glomerulos renales

Mediante la tecnica de Freund se puede obtener una sensibilizacion contra el riñón aun en medio homólogo en este caso la localización del antígeno tisular es la misma pero los correspondientes anticuerpos tisulares (iso o auto anticuerpos) no producen una inflamación comparable a la que provoca la toxina heteróloga Puede sin embargo demostrarse que los efectos de las toxinas bacterianas aun en el caso de una resistencia espontánea elevada (riñón de rata) llegan a manifestarse especialmente en el cortex renal

Asimismo en ciertas condiciones clinicas pero solamente después de una glomerulonefritis se producen modificaciones sericas que indican la formación de anticuerpos no antibacterianos sino contra el cortex renal

No se conoce bien la naturaleza quimica de los antígenos tisulares pero está bien establecido que solamente aparecen en el cortex renal como consecuencia de una inflamación

Este proceso immunológico secundario no se encuentra nada más que en las formas evolutivas progresivas lo cual le da un gran valor para el diagnóstico y pronostico clinicos En los niños no aparece hasta la edad escolar de manera que la evolución hacia una enfermedad cronica es de excepcional rareza en los niños pequeños

No obstante sería un error considerar las nefritis cronicas desde el punto de vista de la auto sensibilización solamente La inflamación renal en los estados eritematoides y en la amilosis renal prueban la gran importancia de factores no solo humorales sino también tisulares Solamente en base a todos estos factores puede determinarse el sentido del desarrollo clinico y patológico de la enfermedad

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COLLAGEN DISEASE IMMUNE AND AUTOIMMUNE MECHANISMS

by

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The allergist has a deep interest in diseases of connective tissue Thus far hypersensitivity has offered the only clue meager though it be to the solution of the pathogenesis of this group of diseases Under this heading I shall include the following conditions polyarteritis nodosa systemic lupus erythematosus (hereafter referred to as SLE) acute rheumatic fever rheumatoid arthritis scleroderma (sometimes referred to as progressive systemic sclerosis or PSS) dermatomyositis and thrombotic thrombocytopenic purpura or TTP These conditions are grouped under one heading because of the following reasons they are of unknown etiology they show involvement of tissues of mesenchymal origin (connective tissue bone muscle cartilage reticulin) they are usually although not always characterized by fibrinoid degeneration of collagen and frequently by hypergammaglobulinemia they have a poor prognosis they result from systemic involvement and show widespread clinical manifestations they universally respond to steroid therapy and finally they are closely related and frequently may be found to merge into and coexist with each other

The evidence for suspecting a possible immunologic basis as a factor in the production of at least some of the diseases of connective tissue is both clinical and experimental On the clinical side may be mentioned the following the frequent association of serum disease with polyarteritis nodosa (2 3) the association of polyarteritis nodosa with intractable bronchial asthma and eosinophilia (4 5 6) and its etiologic relation to various antibiotics and drugs These include penicillin (7 8) dilantin (9) arsenicals (10) thiouracil (11 12 13) foreign serum (14) iodine (15) trichina (16) sulfonamides (17 18 19 20 21 22) mercurials and poison oak (23) Rheumatic fever is occasionally accompanied by urticaria and eosinophilia it is preceded as a rule by infection with streptococcus hemolyticus suggesting the possibility of delayed hypersensitivity it is associated with the presence of antibodies to streptococcal antigens and a positive Coomb s test Finally

the fluid obtained from the involved joints of these patients is sterile Rheumatoid arthritis is thought by many to be also a type of delayed bacterial hypersensitivity Systemic lupus erythematosus (SLE) occurs occasionally in penicillin sensitive individuals These patients demonstrate photo and cold sensitivity Hydralizine employed in the treatment fo hypertension has produced the manifestations of SLE (24 25 26) including the presence of the LE cell and increased gamma globulin changes which disappear once the drug is withdrawn Bacterial hypersensitivity as well as allergy to drugs and sera has been frequently related to SLE (27, 28 29 30 31 32 33) There are instances of thrombotic thrombocytopenic purpura (TTP) in which allergy to sulfonamides penicillin and iodine has been reported (24 38) Some connective tissue diseases are associated with many immunologic phenomena precipitins may be found in polyarteritis nodosa and heterophilic antibodies may be found in SLE Hypergammaglobulinemia characterizes many of these conditions (39) In SLE there is a positive serologic anticomplimentary test for syphilis (40) and frequently *a positive Coomb s test In rheumatic fever there is a high titer antistrep* tolysin O in the serum There is evidence that the gamma globulins are localized in the lesions of polyarteritis nodosa suggesting further in rheumatoid arthritis rheumatic fever and in SLE a possible immune mechanism (41 42) In rheumatoid arthritis there is a factor in the gamma globulin which causes agglutination of the streptococcus and also of sensitized sheep red blood cells In the abnormal gamma globulin found in the serum of patients suffering with collagen disease one finds the following constituents the LE factor and the factor which produces biologic false positive syphilis reactions in the blood of patients with SLE and the rheumatoid agglutinating factor Patients with rheumatoid arthritis and a few perhaps 10 % of patients with SLE especially if they have arthritic manifestations possess an agglutinating factor in their serum This protein factor may agglutinate hemolytic streptococci as well as other organisms They agglutinate sheep red blood cells and may also produce agglutination or precipitation through polystyrene latex fixation thus assuming an antibody like property against human gamma globulin This protein itself is no doubt a gamma globulin In polyarteritis nodosa we probably deal (43 44 45) with an immediate type of sensitivity similar to that in serum disease or anaphylaxis and the Arthus type of lesion However in rheumatic fever the probability is that we are dealing with a delayed type of sensitivity

It would certainly appear then that in *many* instances of connective tissue disease the patients have something in their sera which is not *found in* normal sera

The experimental evidence that connective tissue diseases might possibly be mediated by an immune mechanism while certainly not conclusive is ... are obviously ... egeneration ... d in experimental anaphylaxis and in the Arthus phenomenon (47 48 49) *Masugi* and his associates (49) produced periarteritis nodosa like lesions in sensitized animals with the intravenous injection of egg white Rich and *Gregory* (50) achieved similar results by the injection of *massive* doses of horse serum into rabbits The injection of egg white in mice yielded pathologic changes of

rheumatic carditis (51 52 53 54) Lesions similar to thoses of polyarteritis nodosa have been reproduced not only with horse serum and bovine serum albumin but with egg white and streptococcus toxin (55) Feeding hydralazine to dogs induces in these animals the manifestations of SLE as well as the LE cell phenomenon hematoxylin bodies and characteristic renal pathologic lesions (56) Furthermore antihistaminics will prevent the development of horse serum induced myocarditis an effect similar to that exerted by antihistaminics in protecting animals against anaphylactic shock (57)

Experiments conducted by us in conjunction with others and still in progress add further weight to the assumption as to the the possibility that hypersensitivity plays an important role in the conditions under consideration We shall briefly enumerate our findings

1 We (58) demonstrated that total body x radiation of twenty eight rabbits (600 r and 800 r of x ray radiation) twenty four to seventy two hours before sensitization with horse serum brings about a marked reduction in the number and intensity of vascular lesions and carditis This indicates *an inhibitory action of x ray on the development of the lesions* X radiation of normal non sensitized animals showed no lesions of diffuse vascular disease Previous investigators (59 66) have shown that x ray exerts a definite depressant effect upon antibody production Dammin (67 68) and Bukantz and others noted an inhibition of the production of the Arthus phenomenon and the diffuse vascular lesions of hypersensitivity by the use of nitrogen mustard

2 Bacteria and bacterial products have been implicated in connection with the etiology of rheumatic fever rheumatoid arthritis and occasionally SLE For this reason we (55) were successful in demonstrating the vascular lesions of experimental hypersensitivity by sensitizing a series of rabbits with streptococcus toxin This would seem to be significant in light of the report that postscarlatinal myocarditis results from sensitization to the streptococcus and resembles rheumatic myocarditis (69)

3 In our experiments (70) we found that sera obtained from rabbits fourteen days after sensitization with bovine plasma albumin in animals showing high percentage of vascular lesions and gave patterns characterized by an increase in gamma globulin and decreases in albumin and alpha globulin (fig 1) These results bear a strong similarity to those obtained by Reiner (71) in human beings suffering from SLE

4 We have demonstrated that vascular lesions in experimental hypersensitiveness as well as the hyperglobulinemia thus induced are prevented by cortisone (71 72) and the results are similar to those reported by others (73)

5 Adrenalectomy in our experience enhances the immunologic reactions of hypersensitiveness just as it enhances anaphylaxis the precipitin titer and the severity of the Arthus phenomenon

6 To indicate further the possible immunologic character of the vascular lesions of hypersensitivity we demonstrated in conjunction with Cohen (75) that these vascular lesions may well be induced in normal recipients (rabbits) by passive sensitization By this technique one could eliminate the possibility that the pathologic changes are induced as has been supposed (76 81) by the toxic or nonspecific action accompanying administration of large

doses of foreign serum Chemical agents interfere with this effect of passive sensitization (82) Thus a strong relation seems to exist between the collagen diseases and hypersensitivity (83 1) Thus it is permissible to relate hypersensitivity and immune phenomena to some of the diseases of connective tissue

There is gradually accumulating literature which suggests the possibility

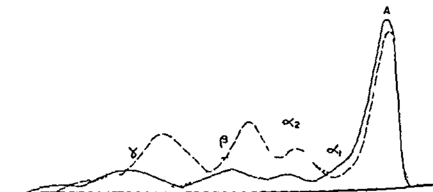


FIG 1 — Electrophoretic pattern in normal (solid) sensitized (broken) and sensitized and cortisone treated animals (dotted)

that an autoimmune mechanism might operate in at least some of the diseases of collagen The evidence thus far available in support of this theory is as will be seen quite meager However, it is provocative By autoimmune mechanism is meant the production of pathologic lesions as a result of a hypersensitivity reaction i e an antigen antibody union the antigen consisting of the host s own tissues These tissues are so affected by various conditions and agents i e infection toxic products etc as to become antigenic and thus give rise to antibodies which in turn combine with the antigen and produce pathologic changes Now this concept at the present time is only a theory Let us examine the present available evidence which warrants speculation in this direction

It is established that in the field of hematology this situation indeed holds good There are many other conditions i e kidney heart thyroid etc in which it has been shown that antibodies to these tissues actually develop and that these antibodies play a role in the production of disease (84 85 86 87 88 89)

Under suitable experimental and occasional clinical conditions demonstrable antibodies develop against many organs of the body i e kidney heart thyroid red blood cells white blood cells platelets etc

Rheumatic Fever complement is fixed according to Brockman Brill and Freud (90 91) by the reaction of antibody containing sera of patients with rheumatic fever with extracts of organs of children who died with this condition Osler et al (92) obtained complement fixation reactions in 50 p 100 of rheumatic fever patients but also in 20 p 100 of normal controls Similarly Vorlaender (93) found in rheumatic fever and rheumatoid arthritis serum complement fixing antibody to heart antigen Cavelti showed by the collodion particle agglutination technic the presence of *in vitro* auto-

antibodies to the rat heart skeletal muscle and rat connective tissue mixed with killed group A Beta hemolytic streptococci (94 95 96) Rejholic and others using the collodion particle agglutination technic demonstrated antibodies in patients with rheumatic fever (97 98) However it should be noted that Fischel (99) and others could not duplicate the finding of auto antibodies by the collodion particle technic Cavelti (96) also reports that the autoantibodies formed combine *in vivo* with the antigenic tissue of the heart and connective tissue following which pathologic lesions develop This author reports (100) serologic reactions using human heart liver and synovial tissues from rheumatic fever patients as well as from normal individuals Vorlaender and his group (101) used the sensitized red blood cells with artery wall antigen and then demonstrated autoantibodies in patients with rheumatic fever by the technic of absorption and hemagglutination of the erythrocytes Autoantibodies to connective tissue were demonstrated in rheumatic fever by Steffen and others absorbing the anti globulin serum in an indirect serological method (102 103) Cardiac lesions similar to those seen in rheumatic fever have been produced experimentally in animals by Robinson (104) He injected subcutaneously multiple doses of serum mixed with streptococci grown in the blood of the same animal He assumes that the lesions are produced by an autogenous antigen antibody complex in which the streptococcus toxin and collagen form the complex antigen Hagerman (105) suspects that the streptococcus in the same manner renders the tissues of the joints and heart muscle antigenic in rheumatic fever so that autosensitization takes place Gamma globulin has been found in the heart lesions of rheumatic fever as well as in various tissues in other diseases of collagen

Rheumatoid Arthritis there is considerable speculation with regards to the possibility that one may deal in this disease with a process of autosensitization It is postulated that connective tissue is rendered antigenic under the influence of infection or that the hyaluronic acid constituent of some bacteria becomes antigenic and thus stimulates antibody formation These antibodies then combine with the endogenous hyaluronic acid The rheumatic nodules in rheumatoid arthritis show the presence of the host s gamma globulin in the central fibrinoid necrotic areas Complement fixation tests (using as antigens extracts of rheumatoid nodules and joint tissue and titrating these against the patient s sera) proved inconclusive The sera of the patients produced precipitation reaction with both rheumatoid and non rheumatoid tissue extracts Hence it would seem that the failure to fix complement suggests that we are not dealing here with an antigen antibody reaction Furthermore rheumatoid sera can precipitate a variety of substances (106)

Systemic lupus erythematosus the *LE cell phenomenon has been* thought by many to be an expression of some form of autosensitization This phenomenon called a pseudo LE cell has been reproduced experimentally with antileukocytic sera through agglutination and phagocytosis Occasionally the phagocyted nucleus undergoes depolymerization giving rise to an LE cell (107) Miescher et al (108 109) indicates that the LE factor is absorbed by isolated nuclei *Apparently there is a definite reaction* between the LE factor and the nucleoprotein This factor reacts with DNA but not with RNA (110 111) This view as to the mechanism of

formation of the LE cell is shared by Heller and Zimmerman (112) and others (113) Mesenchymal cell autoantibodies and a suggestion of an immune phenomenon in the mechanism of the LE cell have been implicated by others (114 115) Vazquez (116) and Dixon demonstrated by immunohistochemical studies using the Coons antibody fluorescence technic presence of the host s gamma globulin in the LE cell and in the spleen and in the wire loop lesions in the kidney without any other plasma proteins The immunologic interpretation of this finding remains as yet to be worked out (116a)

In addition to the LE factor in SLE there are other hematologic manifestations of SLE which suggest the possibility of autoimmune reactions SLE is frequently associated with hemolytic anemia and a positive Coomb s test The red blood cells have undergone certain changes rendering them antigenic and more susceptible to damage and hemolysis What these changes are or what causes them remains as yet obscure They may be brought on by drugs and chemicals acting as haptenes or by other as yet undemonstrable factors The red blood cells become covered with the host s immune globulin which gives a positive test with Coombs antiglobulin serum Evidence seems to indicate that the thrombocytopenic purpura which is found in SLE is not merely a complication of this disease but actually an integral part of it This condition is identical with idiopathic thrombocytopenic purpura which has been amply shown to be mediated by an immunologic mechanism In instances in which it is due to sedormid (117) and quinidine (118 119) an alteration of platelets is caused by the drug probably a haptene so that the platelets become antigenic Thus antiplatelet antibodies are formed In the presence of the particular drug these antibodies destroy platelets causing thrombocytopenia The antibody in immune thrombocytopenia is an agglutinin and possibly a lysin and is usually effective in the presence of complement Dameshek (120) demonstrated that normal platelets are rapidly destroyed when transfused to patients with ITP Harrington et al (121) reports on the development of thrombocytopenia in normal individuals receiving ITP plasma Platelet agglutination tests are known but the clear demonstration and interpretation of platelet antibodies is difficult (122) These findings strongly resemble the situation in autoimmune hemolytic anemia and suggest the possibility that thrombocytopenia of SLE may also be an autoimmune disorder The other blood manifestations of SLE are equally susceptible of suspicion of a possible autoimmune mechanism Thus the leukopenia and neutropenia of SLE may well be mediated by an immune mechanism in which these cells play an important role similar to that seen in drug induced agranulocytosis The positive heterophil agglutination test and the positive serologic test for syphilis may also represent an autoimmune reaction Some instances of SLE present disorders of blood coagulation with hemorrhage (123) Dameshek (124) speculates that when present this may also represent an autoimmune condition in which there occurs an alteration of the clotting mechanism of the blood due to inhibitor susbstances or anticoagulants (123) He reports such a case [illegible] and a reduction in anti[illegible] to whether this may [illegible] or hypoprothrom[illegible]

binemia Many autoantibodies have been described as present in this disease i e autoantithromboplastin (125 126) hemolysins (127 128 129) erythrocyte agglutinins (130 131) Gajdusek (132) demonstrated complement fixation as taking place in the reaction between the gamma globulin of patients with SLE and normal tissue extracts acting as antigens According to Bywaters and others (133) SLE may also show the formation or iso agglutinins following blood transfusion The evidence as to the autoimmune character of the blood vessel lesion in SLE is more restricted even though some (124 134 135) have indulged in much speculation in this connection suspecting that the lesions in the kidney spleen skin and pleura may also be of an autoimmune character However thus far it has been impossible to detect antibodies against connective tissue or blood vessels nor do we have any knowledge as to what the antigen is immune or autoimmune which may play a role in the pathogenesis of this disease

The same type of phenomenon may be suggested as taking place in thrombotic thrombocytopenic purpura accompanied as it is by hemolytic anemia thrombocytopenic purpura and involvement of arterioles although no antibodies against red blood cells and against platelets have been found in this condition

Dermatomyositis may be associated with carcinomatosis It is postulated by Kurnick (136) that this condition arises as a result of the formation of autoantibodies to the neoplasm autoantibodies which react with other tissues This cross reaction may give rise to pseudo LE cells and even the lesions of dermatomyositis

The tissues primarily involved in collagen disease are connective tissue and muscle With respect to the former there is little support for the assumption that connective tissue or any of its constituents may become antigenic in these conditions Any efforts made to confirm the occurrence of antibodies to such connective tissue components as hyaluronic acid collagen or chondroitin sulphuric acid have been unsuccessful In these instances both homologous or heterologous materials have been employed (137)

While the theory of a possible causal relation of hypersensitivity to at least some of the diseases of collagen is attractive it is supported only by circumstantial evidence and therefore justifies no definite conclusions Similar pathology does not necessarily denote similar pathogenesis or similar etiology The fact remains that thus far no one has demonstrated a definite antigen which will produce the clinical manifestations of collagen disease nor an antibody to this antigen nor proof that the lesions result from antigen antibody union If the evidence as to the immune nature of collagen disease is meager then the evidence in connection with the auto immune mechanism of these conditions is even more doubtful It is of a nature that permits at this time only further speculation in the hope that it may stimulate much needed study of this group of exciting and baffling diseases

SUMMARY

The allergist has a deep interest in diseases of connective tissue To be considered are the following conditions polyarteritis nodosa systemic lupus erythematosus acute rheumatic fever rheumatoid arthritis scleroderma dermatomyositis and thrombotic thrombocytopenic purpura

The clinical evidence as to a possible immunologic mechanism in these conditions may be summarised as follows

The association of serum disease with polyarteritis the association of polyarteritis nodosa with asthma its causal association with drugs the association of rheumatic fever with urticaria and eosinophilia, with preceding infection and with the presence of antibodies to the streptococcus S L L manifestations are reproduced by hydralazine Furthermore many immunologic and serologic phenomena are found in some of the conditions and gamma globulin has been shown to localize in the lesions

Experimentally the following has been shown the finding of fibrinoid degeneration in experimental serum disease anaphylaxis the Arthus phenomenon and in many of the collagen diseases the reproduction of these pathologic lesions by experimental sensitization and by administration of hydralazine in dogs the prevention of horse serum myocarditis by antihistaminics Experiments conduced by us reveal the following 1 Total body x radiation of rabbits reduces the vascular lesions produced by sensitization an effect similar to the action of nitrogen mustard 2 Streptococcus toxin sensitization produces typical vascular lesions 3 Hypergammaglobulenemia ressembling that seen clinically in collagen disease is found in the experimentally produced allergic vasculitis 4 The lesions and the hypergammaglobulenemia are reduced and prevented by steroids 5 Adrenalectomy in rabbits enhances these phenomena of sensitization 6 The vascular lesions may be induced by passive sensitization

The evidence in connection with the auto immune nature of these conditions is even more meager

Rheumatic fever It is therefore theorized that infection with the streptococcus brings about a change in the myocardium which renders it antigenic leading to the formation of anti myocardial auto antibodies

Rheumatoid arthritis In this condition again it is postulated that connective tissue is rendered antigenic because of infection or metabolic influences

Systemic lupus erythematosus The mechanism of formation of the L E cell suggests the possible antigenicity of cell nuclei especially since a pseudo L E cell has been reproduced with anti leucocytic sera gamma globulin is shown to localize in the L E cell positive Coombs test in S L E in the presence of auto immune hemolytic anemia the finding of other auto immune antibodies in this disease the presence of complement fixation using the gamma globulin of patient with S L F and normal tissue extracts

Dermatomyositis It is postulated since many of these patients have carcinomatosis that there may develop in this condition sensitization to the neoplastic tissue

While the theory of a possible causal relation of hypersensitivity in at least some of the diseases of collagen is attractive it is supported only by circumstantial evidence and therefore justifies no definite conclusions

RÉSUMÉ

Les maladies des tissus conjonctifs presentent un interet considerable pour l allergologiste Les maladies entrant en ligne de compte sont *la periarterite noueuse le lupus erythemateux dissemine le rhumatisme articulaire aigu le rhumatisme chronique deformant la sclerodermie la dermatomyosite le purpura thrombotique thrombocytopenique*

On peut résumer ainsi les preuves cliniques que nous possedons de l intervention possible d un mecanisme immunologique dans ces états pathologiques

— Association de la *maladie serique* a la *périarterite noueuse*

— Association de la *periarterite noueuse* a *l asthme* et sa determination par certains medicaments

— Association du *rhumatisme articulaire aigu* a *l urticaire* et a *l eosinophilie* apres une infection et en présence d anticorps aux streptocoques

— La possibilite de recreer par l hydralazine les manifestations du *lupus erythémateux disséminé*

— De plus de nombreux phenomenes serologiques et immunologiques ont éte notes au cours de certaines de ces maladies

— Il a ete demontre que la gamma globuline se localise dans les lesions

Des expériences ont démontre ce qui suit

On observe une dégénerescence fibrinoide pendant la maladie serique experimentale l anaphylaxie le phenomene d Arthus et aussi au cours d un grand nombre de maladies du collagene

La possibilité de reproduire chez les chiens par l administration d hydralazine et par sensibilisation experimentale ces lesions pathologiques

La prevention de la myocardite produite par l injection de serum de cheval par les anti histaminiques

Des experiences faites par l auteur lui meme ont revele les faits suivants

1° L irradiation totale par rayons X des lapins réduit les lesions vasculaires dues a la sensibilisation et produit un effet analogue a celui de la moutarde a l azote

2° La sensibilisation a la toxine streptococcique produit des lesions vasculaires caracteristiques

3° Une hyper gammaglobulinémie ressemblant a celle cliniquement observée dans les maladies du collagene se produit dans l angéite vasculaire expérimentalement provoquee

4° Les lésions et l hyper gammaglobulinemie peuvent etre reduites et empechees au moyen des stéroides

5° Chez les lapins la surrenalectomie intensifie ces phénomenes dus a la sensibilisation

6° Les lésions vasculaires peuvent etre provoquées par sensibilisation passive

Les preuves auto immunologiques de ces maladies sont encore peu nombreuses

Rhumatisme articulaire aigu pour ces raisons on peut admettre théoriquement que les infections à streptocoques provoquent une modification du myocarde qui devient antigénique ce qui amène la formation d'autoanticorps dirigés contre lui

Polyarthrite rhumatismale évolutive là encore, on peut admettre que le tissu conjonctif devient antigénique sous l'influence de l'infection et de facteurs métaboliques

Le lupus érythémateux disséminé le mécanisme de formation de la cellule L E donne à penser que le noyau cellulaire est peut être antigénique plus particulièrement du fait qu'il a été possible de recréer au moyen de sérums anti leucocytaires une cellule pseudo L E

Il a été démontré que la gammaglobuline se localise dans la cellule L.E. Lorsqu'il existe une anémie hémolytique auto-immune le test de Coombs est positif dans le lupus érythémateux disséminé

D'autres anticorps auto immuns ont été trouvés au cours de cette maladie

La mise en contact d'extraits tissulaires provenant d'individus normaux avec la gammaglobuline d'un malade atteint de lupus érythémateux produit une fixation du complément

Dermatomyosite comme beaucoup de malades atteints de cette maladie présentent aussi des symptomes de carcinomatose on peut supposer qu'il y a dans cette maladie une sensibilisation au tissu néoplasique

Bien que séduisante la théorie selon laquelle il y aurait des relations de cause à effet entre l'hypersensibilisation et au moins quelques maladies collagènes n'est appuyée que sur des preuves circonstancielles et il est impossible d'en tirer des conclusions définitives

ZUSAMMENFASSUNG

Die Allergologisten haben an den Bindegewebserkrankungen grosses Interesse Folgende Erkrankungen werden in Erwägung gezogen. *Periarteritis nodosa Lupus erythematodes disseminatus akutes Rheumafieber rheumatoide Arthritis Scleroderma Dermatomyositis und thrombotische thrombocytopenische Purpura*

Folgende klinische Erfahrungen lassen immunologische Mechanismen bei diesen Erkrankungen vermuten

Verbindung von Serumkrankheit und Periarteritis Verbindung von Periarteritis nodosa mit Asthma deren Kausalzusammenhänge mit Drogen die Verbindung von rheumatischen Fieber mit Urticaria Eosinophilie

[illegible] Antikorpern

[illegible] nen

[illegible] sen

[illegible] den

Krankheiten einige immunologische und serologische Phänomene [illegible] und die Lokalisierung von Gamma Globulinen in den Läsionen konnte aufgezeigt werden

Experimentell konnte gezeigt werden Auftreten von fibrinoider Degeneration bei experimenteller Serumkrankheit Anaphylaxie Arthus Phänomen und bei vielen der Bindegewebserkrankungen Reproduktion dieser pathologischen Läsionen durch experimentelle Sensibilisierung und durch

Hydralazingabe bei Hunden Verhutung von Pferdeserummyocarditis durch Antihistamine Von uns durchgefuhrte Experimente zeigten folgende Ergebnisse

1 Rontgenbestrahlung des Gesamtkorpers von Kaninchen reduziert die vaskularen Lasionen die durch Sensibilisierung bedingt sind und ahnelt so der Wirkung von Stickstoff Lost 2 Streptokokkentoxin sensibilisierung zeitigte typische Gefasslasionen 3 Eine Hypergammaglobulinamie ahnlich der klinisch bei Bindegewebserkrankungen gefundenen konnte bei experimentell erzeugter allergischer Vasculitis nachgewiesen werden 4° Die Lasionen und die Hypergammaglobulinamie werden durch Stereoide vermindert oder vermieden 5° Die Enfternung der Nebennieren vergrossert bei Kaninchen diese Sensibilisierungsphanomene 6° Gefasslasionen konnen durch passive Sensibilisierung hervorgerufen werden

Über eine mogliche Auto Immun Natur dieser Erkrankungen ist noch wenig bekannt

Rheumatisches Fieber es wird die Theorie augfestellt dass die Streptokokkeninfektion eine Änderung des Myocards bedingt so dass dieses nunmehr antigen wird und die Bildung von Antimyocard Autoantikorpern bewirkt

Rheumatische Arthritis auch bei dieser Erkrankung wird angenomen dass das Bindegewebe durch Infektionen oder Stoffwechselstorungen so verandert wird dass es nachher antigen i t

Lupus erythematodes disseminatus Der Mechanismus der L E Zellbildung lasst vermuten dass moglicherweise die Zellkerne antigen sein konnten besonders seit der Reproduktion von Pseudo L E Zellen mittels antileukozytaren Seren Gammaglobulin konnte in den L E Zellen nachgewiesen werden positiver Coombstest bei Lupus erythematodes disseminatus bei Vorhandensein einer auto immunen hamolytischen Anamie das Auffinden von anderen auto immunen Antikorpern bei dieser Erkrankung Auftreten einer Komplementbindung bei Verwendung von Gamma Globulinen an S L E erkrankter Patienten und normalen Gewebs extrakten

Dermatomyositis da viele der Patienten eine Carcinomatose haben wird vermutet dass bei dieser Erkrankung eine Sensibilisierung gegen das neoplastische Gewebe auftreten konnte

Wenn auch die Theorie eines möglichen Kausalzusammenhanges zwischen einer Überempfindlichkeit und wenigstens einiger dieser Bindegewebserkrankungen vieles fur sich hat so ist sie doch nur auf Indizienbeweise gestutzt und berechtigt daher nicht auf entgultige Schlusse

RESUMEN

El alergista está profundamente interesado en las enfermedades del tejido conectivo que incluyen *periarteritis nodo a lupus eritematoso fiebre reumática aguda artritis reumatoide esclerodermia dermatomiositis y purpura trombopénica*

La evidencia clínica en favor de un mecanismo immunológico es la siguiente la asociación de enfermedad del suero y periarteritis la asociación de periarteritis nodosa y asma también con drogas la asociación de fiebre

reumática con urticaria y eosinofilia precedida de una infección y con anticuerpos antiestreptococos Además los síntomas de SLE pueden ser producidos por hidralizina, muchos fenómenos inmunológicos y serológicos aparecen en varias de las enfermedades citadas y se ha podido demostrar la localización de gama globulina en las lesiones

Experimentalmente se ha encontrado una degeneración fibrinoide en la enfermedad del suero experimental el fenómeno de Arthus la anafilaxia y muchas enfermedades del colágeno estas lesiones se han podido reproducir en el perro por administración de hidralizina y tambien durante la sensibilización experimental y la miocarditis causada por suero de caballo ha podido ser evitada por el uso de antihistamínicos Experiencias realizadas por los autores indican 1º Irradiación total del cuerpo en el conejo por rayos X reducen las lesiones vasculares producidas por sensibilización un efecto similar al de la mostaza nitrogenada, 2º la sensibilización con toxina estreptocóccica produce lesiones vasculares típicas 3º la hipergamaglobulinemia encontrada en la vasculitis alergica experimental es clínicamente semejante a la que se ve en las enfermedades del colágeno 4º tanto las lesiones como la hypergamaglobulinemia pueden ser reducidas o evitadas por los esteroides, 5º la extirpación de las suprarrenales en el conejo acentua e tos fenómenos y 6º las lesiones vasculares pueden ser provocadas por sensibilización pasiva

La evidencia sobre la naturaleza auto inmune de estas enfermedades es todavía mas escasa

Fiebre reumatica Se supone que la infección estreptocóccica produce modificaciones en el miocardio que lo hacen antigenico formándose entonces anticuerpos anti miocardio

Artritis reumatoide Se supone tambien que por infeccion o influencias metabólicas el tejido conectivo se hace antigenico

Lupus eritematoso sistemico El mecanismo de formación de la célula LE sugiere la posible antigenicidad del nucleo celular se ha podido demostrar la localización de gama globulina en la célula LE, el test de Coombs es positivo en el SLE en presencia de anemia autohemolitica también se han encontrando otros anticuerpos auto immunes en esta enfermedad y se ha encontrado una fijación de complemento utilizando gama globulina de pacientes con SLE y extractos de tejidos normales

Dermatomiositis Como muchos pacientes tienen carcinomatosis, se ha postulado la sensibilización al tejido neoplásico

El autor considera que si bien hay evidencias en favor de una relación causal entre la hipersensibilidad y algunas enfermedades del colageno no se justifican por el momento conclusiones definitivas

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LE LUPUS ÉRYTHÉMATEUX DISSÉMINÉ LE PHÉNOMÈNE L.E. ET LES SÉRO-RÉACTIONS ANTI-SUBSTANCES NUCLÉAIRES

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Le lupus érythémateux disséminé est connu depuis des années comme une affection s'accompagnant facilement des sensibilisations à l'égard de différents antigènes et tout particulièrement des iso-antigènes des groupes erythrocytaires, y compris ceux possédant une faible antigénicité (Callender (1), 1945/46). Depuis lors une multiplicité d'immuno-réactions a été observée dans cette affection. On a été particulièrement frappé par la fréquence d'auto-anticorps cellulaires à l'égard de tissus les plus divers : anticorps contre noyaux, erythrocytes, thrombocytes, facteurs de coagulation (*VIII, IX, thromboplastine*), rein, cœur, foie. Signalons enfin l'existence de certains phénomènes qui se rattachent à des réactions auto-immunes : réaction de Wassermann positive, l'hémagglutination d'hématies de mouton sensibilisées (18).

De tous ces phénomènes, celui découvert par Hargraves, Richmond et Morton (6) en 1948 et appelé phénomène L.E. a retenu la plus grande attention, étant donné sa *spécificité dans cette affection*. Nous résumons brièvement ses caractéristiques : le facteur L.E. est une gamma-globuline de faible mobilité électrophorétique ayant un point iso-électrique relativement élevé qui se présente à l'ultracentrifugation comme un composant du type 7S (4). Ce facteur est responsable du phénomène L.E. : sous son influence les leucocytes subissent des altérations spécifiques constituées par la perte partielle de la basophilie du noyau, son gonflement et l'effacement de sa structure chromatinienne ; le cytoplasme se détache de ces noyaux « homogénéisés ». D'autres leucocytes intacts enveloppent ces corps *nucléaires libres et forment ainsi les cellules « L.E. ». Celles-ci sont* des leucocytes neutrophiles présentant en général un noyau repoussé à l'extrémité de la cellule par une masse importante polychromatique et ayant une structure diffuse plus ou moins homogène. En se basant sur des études

(*) Avec l'aide de la Fondation E. Barell, Bâle. Nous remercions Mlle M. Fauconnet et M. H. Br gatsch de leur collaboration.

histio himiques Klemperer et coll (11) ont supposé que la modification nucléaire consiste en une dépolymérisation des acides désoxyribonucléiques Or cette hypothese encore admise par la plupart des cliniciens a du etre abandonnee par Klemperer lui meme et son ecole en 1956 (12)

En clinique la spécificite du phénomène L E a ete mise en doute par différents auteurs On a du reconnaitre cependant que la plupart des phenomènes L E rencontres dans des affections autres que le lupus erythemateux disséminé (L E D) ont des caracteres morphologiques particuliers qui permettent de les differencier du « vrai » phénomene C est pour cette raison que nous avons proposé de designer ceux ci comme des « pseudo phenomènes L E » (2) il s agit habituellement de « Tartcells » c est a dire des phagocytes le plus souvent neutrophiles contenant des noyaux lymphocytaires non homogénéisés et encore tres basophiles On n observe pas les modifications intracellulaires décrites plus haut

Apres avoir éliminé les pseudo phénomenes L E il reste tout de meme deux affections au cours desquelles le phénomene L E peut etre observe et dont les criteres morphologiques correspondent à ceux decrits dans le lupus erythemateux disseminé *a)* L apresoline (compose du type de l hydralazine) a fortes doses peut provoquer chez certains malades un syndrome tres analogue au lupus érythémateux disseminé la plupart de ces malades présentent a l examen un phénomène L E typique (3 21 4) *b)* Enfin on a signalé au cours de la polyarthrite chronique evolutive (P C E) l apparition de ce phenomène typique dans un pourcentage qui varie d un auteur a l autre (5 7 9 10 20 25 30)

Pour preciser les différentes questions soulevées par l apparition du phénomene L E il nous a paru indispensable de faire des *etudes serologiques* Nous savons en effet que l expression morphologique des cellules et des tissus est limitee et que différents processus pathogéniques peuvent aboutir au meme tableau morphologique

Apres avoir démontre que le facteur L E peut etre absorbé par des noyaux cellulaires isoles (13) et en etre élué apres fixation nous sommes parvenus a le mettre en évidence par la *reaction de consommation de l anti globuline* (15) Cette reaction s est averée tres sensible Le facteur L E reagit egalement avec des noyaux cellulaires d origine animale (17) Le tissu dont les noyaux ont eté isolés est indifferent En pratiquant ce test avec des noyaux cellulaires isoles de tissus on peut ainsi differencier le facteur L E des leuco agglutinines qui peuvent coexister avec lui et qui reagissent avec le cytoplasme des leucocytes et parfois avec des noyaux leucocytaires en raison des substances cytoplasmatiques qui n ont pu etre éliminees

Le resultat de nos etudes sur l antigenicite du noyau cellulaire (14 16) nous a incite a developper d autres reactions serologiques La sensibilisation expérimentale d animaux par des constituants antigeniques du leucocyte polynucleaire a montre que le cytoplasme est responsable de la specificite antigenique du leucocyte Le noyau du leucocyte pour sa part possede une autre spécificité qu il partage avec d autres noyaux cellulaires et qui n est donc pas liee au seul leucocyte *Les nucleoproteines sont indispensables a cette spécificité* (16)

En appliquant ces données a la sérologie du lupus érythemateux disseminé il a pu etre démontre en effet que le facteur L E peut etre absorbé sur des nucleoproteines d origine animale et que par conséquent le test de

consommation de l antiglobuline peut etre effectue avec la *nucleoproteine* qui est une substance tres peu soluble (7) *L acide desoxyribonucleique (DNA)* constitue on le sait la substance fondamentale des nucleoproteines Par des essais d absorption on a montre que le facteur L E peut également etre en partie absorbé sur l acide desoxyribonucleique tandis qu on obtient des résultats négatifs avec l acide ribosenucleique Les tests d absorption avec l acide désoxyribonucléique sont moins faciles a effectuer que ceux avec la nucléoprotéine à cause du pH acide de l acide desoxyribonucléique et de sa grande solubilite En appliquant la technique de l hémagglutination passive il a pu etre demontré qu un serum contenant le facteur L E agglutine des erythrocytes de mouton qui ont ete prealablement traités avec l acide tannique et recouverts de nucleoprotéine ou d acide désoxyribonucléique (19) Actuellement nous nous servons de la *reaction de particules de latex* pour mettre en evidence ces reactions Cette technique donne de meilleurs résultats

D autres auteurs ont signale dans des publications simultanees ou posterieures une réaction entre le serum L E et l acide désoxyribonucleique (8 23 26 27 28) Polli et coll (23) et Seligmann (26) ont mis en evidence cette reaction par une methode de precipitation Seligmann et Milgrom par une deviation du complément (27) Holman et Kunkel sont arrives a la meme conclusion par des methodes indirectes (8) Tout recemment Seligmann et Robineaux (28) ont dissocie le complexe facteur serique acide desoxyribonucleique et ont pu montrer que ce facteur est bien capable de provoquer le phenomene L E en presence de serum normal Ceci prouve d une façon directe que c est bien le facteur L E qui est mis en jeu

Avec ces reactions serologiques nous possedons de nouveaux moyens pour preciser la spécificite du phenomene L E et pour distinguer les pseudo phenomènes L E Dans ce but nous avons examine le sang de malades atteints de polyarthrite chronique évolutive et de lupus érythemateux disseminé Deux groupes servaient de temoins l un comportant des malades atteints d affections articulaires dégeneratives l autre des malades atteints d affections variees non articulaires

MÉTHODES

A ***Phenomène L E d après la methode de Zimmer et Hargraves*** (31)

B ***Épreuve de consommation de l antiglobuline par les noyaux cellulaires isolés*** (voir fig 1) (15 18)

Cette seconde epreuve est basee sur le principe que les cellules chargees d anticorps (facteur L E = gammaglobuline humaine) fixent les anticorps antiglobulines humaines et peuvent ainsi diminuer le titre d un serum antiglobuline

1 *Preparation des noyaux cellulaires isoles* (16) Pour les recherches actuelles nous avons utilise les noyaux cellulaires isolés du thymus de porc

2 *Réaction entre les noyaux cellulaires et le facteur L E supposé du serum du malade* 10 mg de noyaux lyophilisés sont suspendus dans 1 ml du sérum du malade et 1 ml de serum physiologique Apres une incubation

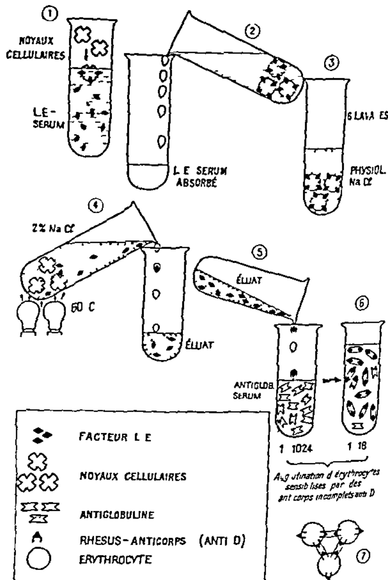


FIG 1 — Presentation schématique du test de consommation d antiglobuline

1 Un ml de sérum + 8 mg de noyaux cellulaires lyophilisés Un controle est toujours fait avec du sérum normal Mettre à 37 °C pendant trente minutes

2 Centrifuger et décanter le serum.

3 Mettre en suspension les noyaux cellulaires dans de l eau physiologique glacée et les laver jusqu à ce que la solution d eau physiologique soit exempte d albumine (laver 6 a 7 fois)

4 Noyaux cellulaires + o 5 ml d une solution de NaCl à 2 p 100 mettre d abord a 4 C pendant dix minutes puis au bain marie à 60 °C pendant vingt minutes centrifuger les noyaux apres l incubation à chaud

5 Decanter l éluat surnageant

6 Melanger à parties egales l eluat et le sérum antiglobulinique Les differentes dilutions du sérum antiglobulinique ne sont pas dessinees sur le schema, elles doivent être melangees separement à l eluat

7 Test de Coombs pour la determination du titre du serum antiglobulinique (Agglutination d erythrocytes sensibilises par des anticorps incomplets anti D)

de trente minutes a 37° C les noyaux sont laves sept fois a la temperature de 4° C avec du sérum physiologique (ou avec une solution glacée d eau physio logique dans une centrifugeuse ordinaire) Le culot nucléaire ainsi lavé est ensuite mis en suspen ion dans 0 5 ml d une solution à 2 p 100 de NaCl Apres avoir bi n mélangé la suspension nucléaire on l incube pendant dix minutes à 4° C On met la suspension dans un bain marie a 60° C en l agitant toutes les cinq minutes Au bout de vingt minutes on centrifuge à grande vitesse la suspension de noyaux cellulaires dans un recipient préala blement chauffé à 60° C Ensuite le liquide exempt de cellules est soutire au moyen d une pipette et soumis à l epreuve de consommation (voir plus loin)

3 *Sensibilisation d erythrocytes O Rh + avec un serum anti D* deux gouttes de sédiment d érythrocytes sont mises en suspension dans trente gouttes de solution physiologique et mélangees avec dix gouttes d un serum anti D d un titre d environ 1 512 Le mélange est incube pendant trente minutes a 37° C Apres trois lavages avec solution physiologique les hématies sont remises en suspension dans ce liquide à la concentration d environ 5 p 100 en volume

4 *Épreuve de consommation proprement dite* Dans chaque quadrant d une plaque de verre opaque divisée en 24 quadrants et chauffee à 37 °C une goutte de l eluat est mélangee avec une goutte d un serum antiglobuline puissant a six concentrations differentes (on choisit les concentrations du sérum antiglobuline de telle sorte que la plus grande des dilutions qui suivent une progression géométrique de 0 5 donne tout juste une hémagglu tination positive de cellules chargées d anticorps incomplets du systeme Rhésus) Après trois minutes on ajoute à chaque goutte une goutte de la suspension preparee d érythrocytes O Rh+ chargés d anticorps incomplets anti D et l on mélange soigneusement Exactement cinq minutes plus tard on lit le résultat La consommation de l antiglobuline se manifeste par une diminution du titre du sérum antiglobuline apres contact avec l éluat

En pratique on compare toujours le résultat obtenu avec un sérum pathologique avec celui obtenu avec un sérum normal Dans le cas d un test positif les érythrocytes sensibilisés sont agglutinés par le mélange serum antiglobuline éluat pathologique a un titre moins élevé qu avec le mélange sérum antiglobuline éluat normal et les agglutinations érythro cytaires sont plus discretes dans les concentrations plus fortes de l anti globuline 1+ diminution d un titre 2+ diminution de 2 titres 3+ diminution de 3 titres etc (par exemple titre avec l eluat normal 1 1 024 Titre avec l éluat pathologique 1 512 = 1+ 1 256 = 2+ 1 128 = 3+ etc)

C *Test d agglutination de particules de latex*

Le principe de cette technique élaborée par Plotz et Singer (22 29) est le suivant une suspension de particules de latex sert d indicateur de la réaction antigene anticorps On prépare une suspension ayant une faible stabilité de sorte qu un changement peu important du milieu ambiant suffit a agglutiner les particules Nous avons adopté cette méthode pour mettre en évidence une réaction entre un sérum L E et l acide désoxyri bonucleique ou une nucléoprotéine La reaction d agglutination des parti

cules de latex s est montrée supérieure à l hémagglutination passive et à la réaction de précipitation En ce qui concerne l hémagglutination passive il est possible que la fixation de l acide désoxyribonucleique ou de la nucléoprotéine aux érythrocytes tannés soit défectueuse

MATÉRIEL 1 *Suspension à 11 p 100 de particules de latex ayant un diamètre de particules de 0 814 + 0 0105 micron* (Polystyrene latex de Dow Chemical Company Midland Michigan) (*) 1 ml de cette suspension est amené à un volume de 10 ml avec de l eau bidistillée Cette suspension est centrifugée à 2 300 tours/minute pendant trois minutes pour en éliminer les agglomérats Le liquide surnageant est filtré à travers un filtre Whatman n° 40 La préparation ainsi obtenue peut être gardée pendant plusieurs semaines au froid (à 4° C) L intensité du trouble de la suspension doit être telle qu après dilution de 1 100 avec du tampon au glycocolle (voir plus loin) l intensité d une lumière de 578 mÅ transmise à travers une couche de 10 mm soit égale à 20 p 100 de la quantité de lumière reçue

Nous employons des particules de diamètres différents suivant l antigène

Réaction avec l acide désoxyribonucléique particules de 0 814 ± 0 0105 micron

Réaction avec de la nucléoprotéine particules de 1 17 ± 0 0133 micron

Réaction avec de la gammaglobuline particules de 1 17 ± 0 0133 micron.

2 *Tampon au glyco olle (glycine)* à un pH de 8 2 751 mg de glycocolle sont dissous dans 100 ml d eau bidistillée (solution 0 1 M) On y ajoute environ 0 25 ml d une solution In de NaOH et on ajuste le pH à 8 2 avec la solution de NaOH On incorpore ensuite 1 g de NaCl et 0 1 g d acide de sodium (N_3Na) Cette dernière substance fait fonction d antiseptique pour les réactions sérologiques

3 *Solutions antigéniques*

a) Acide désoxyribonucléique (DNA) Nous employons de l acide désoxyribonucleique isolé de thymus de veau Mais des acides désoxyribonucléiques d autres provenances peuvent également être employés 1 mg d acide désoxyribonucléique est dissous dans 100 ml de tampon au glycocolle (pour des essais spéciaux on peut utiliser d autres concentrations)

b) Nucléoprotéine Nous employons une nucléoprotéine isolée de thymus de veau mais la provenance de cette substance n a pas une grande importance Des expériences avec de la nucleoprotéine d origine bactérienne sont en cours Il est cependant préférable de ne pas les employer pour les tests de routine On dissout 2 5 mg de nucléoprotéine et 0 3 g de NaCl dans 100 ml de tampon au glycocolle (concentration 25 gamma nucléoprotéine par ml)

c) Gammaglobuline (**) Des gammaglobulines individuelles ne s adaptent pas à cette réaction à cause des groupes Gm qui interviennent dans la réaction avec le facteur rhumatoide Pour cette raison on travaille de

(*) Nous remercions le Dr John W Vanderhoff de Physical Research Laboratore The Dow Chemical Co d avoir mis à notre disposition les particules de latex

(**) Nous ... Central du Centre National de ... e Dr S Gibson Directeur de ... A d avoir mis à notre disposition de la gammaglobuline humaine

preference avec une gammaglobuline isolée a partir d un grand nombre de plasmas humains par fractionnement selon la methode de Cohn 0 1 g de gammaglobuline est dissout dans 10 ml de tampon au glycocolle (solution a 1 p 100) Cette solution peut etre gardee a 4° C pendant des semaines Avant d effectuer le test 0 5 ml de cette solution stock est dilue avec 9 5 ml de tampon au glycocolle

4 *Technique d agglutination de particules de latex* Le serum pathologique et le sérum temoin sont dilués avec le tampon au glycocolle depuis la dilution 1 2 jusqu à la dilution 1 256 (pour les tests de routine il suffit d arreter les dilutions a 1 32) Immediatement avant de faire ce test on ajoute 0 1 ml de la suspension de latex a 10 ml de la solution antigenique On mélange 4 gouttes de sérum a ces diverses dilutions avec 4 gouttes de la solution antigenique contenant les particules de latex (tubes 8 × 60 mm) Temoins serum avec particules de latex sans l antigene particules de latex chargees d antigene sans le sérum

Apres un melange soigneux les tubes sont incubes dans un bain marie pendant 90 minutes a une temperature de 56° C pour la gammaglobuline et de 37° C pour l acide désoxyribonucléique et la nucleoproteine Ils sont ensuite incubes a 4 °C pendant la nuit La lecture est faite le lendemain au microscope en examinant une goutte provenant de chaque tube Le resultat est considéré comme positif s il y a une agglutination des particules de latex a un titre du serum de 1 2 pour l acide desoxyribonucleique et la nucleoproteine 1 40 pour la gammaglobuline a condition qu il n y ait pas d agglutination dans les tubes de controle

RÉSULTATS

Le resultat sommaire des examens serologiques est reuni dans le tableau I les resultats de quelques cas individuels dans le tableau II

Parmi les seize malades atteints de *lupus erythémateux dissemine* et presentant un tableau clinique caractéristique de cette maladie on a observe cliniquement chez quatorze d entre eux un phenomene L E typique Dans un cas la morphologie de ce phenomene ne correspondait pas a tous les criteres tout en etant suspect (pseudo phenomene L E) En ce qui concerne les autres tests serologiques les resultats n etaient pas constants Dans les tableaux I et II nous n avons pas tenu compte de ce fait et considéré un test comme positif meme s il ne l etait qu une fois En ne testant un malade qu une seule fois le pourcentage de ces resultats sera donc plus faible Le test le plus sensible etait celui de la consommation de l antiglobuline sur noyaux Ce qui a frappe dans ce groupe ce n était pas seulement la régularite avec lequel ce test etait positif mais également son intensite L éluat des noyaux cellulaires diminuait tres fortement le titre d un sérum antiglobuline En dehors du lupus erythémateux dissémine il n y avait qu une tres faible consommation dans les quelques tests positifs de consommation de l antiglobuline sur noyaux Enfin le facteur rhumatoide a ete mis en évidence chez trois malades seulement

Chez sept malades le diagnostic clinique de lupus erythemateux dissemine n était pas certain en raison d une evolution atypique exempte d éruptions

TABLEAU I

Resultat des réactions sérologiques Les valeurs en p 100 sont mises entre parenthèses

DIAGNOSTIC	NOMBRE DE CAS	PHÉNOMÈNE L E			CONSOMMATION DE L ANTIGLOBULINE SUR NOYAUX CELL		AGGLUTINATION DE PARTICULES DE LATEX					
							Ac. désoxyribonucléique		Nucléoprotéine		Gammaglobuline	
		posit	pseudo	négat	posit	négat	posit	négat	posit	négat	posit	nég
Lupus érythémateux disséminé	17	15 (88)	1 (6)	1 (6)	17 (100)	0 (0)	11 (65)	6 (35)	14 (82)	3 (18)	3 (18)	14 (82)
Lup éryth disséminé probable	7	0 (0)	6 (86)	1 (14)	5 (72)	2 (28)	4 (57)	3 (43)	3 (43)	4 (57)	2 (28)	5 (72)
Lup éryth localisé	2	0	0	2	0	2	1	1	0	2	0	5
Aprésoline L E D	1	1	0	0	1	0	—	—	—	—	—	—
Polyarthrite chronique évolutive	51	5 (10)	9 (18)	37 (74)	7 (14)	44 (68)	11 (22)	40 (78)	2 (4)	49 (96)	35 (63)	16 (31)
Syndrome de Kaplan	4	0	0	4	0	4	0	4	0	4	2	2
Spondyl arthrite	1	0	0	1	0	1	0	1	0	1	0	1
Affections articul dégénérat	25	0 (0)	0 (0)	25 (100)	0 (0)	25 (100)	1 (4)	24 (96)	0	25 (100)	1 (4)	24 (96)
Affections variées	25	0 (0)	1 (4)	24 (96)	0 (0)	25 (100)	1 (4)	24 (96)	1 (41)	24 (96)	1 (4)	24 (96)

Le sang de plusieurs malades a été examiné à différentes reprises au cours d'évolution de la maladie Dans ce tableau nous n avons pas tenu compte de la question de savoir si un résultat a été trouvé toujours positif ou seulement une fois En soignant des malades atteints de lupus erythémateux disséminé il a été souvent observé que l intensité des réactions serologiques diminue ou que les résultats deviennent négatifs En n examinant qu une seule fois ces malades le pourcentage de réactions positives sera donc plus faible

Nous remercions les Dr H Enderlin et U Steiger (clinique universitaire de rhumatologie (Directeur Prof A Boni) Zürich) Irving A Friedman (Ass t Director of the Hektoen Institute for Medical Research of the Cook County Hospital Chicago Illre) J J van Loghem jun (Directeur du Centre National de Transfusion Sanguine de la Croix Rouge Amsterdam) H Schmid (Direc eur de la clinique m^dicale de Schaffhouse) et A Vannotti (Directeur de la clinique médicale universitaire de Lausanne) de nous avoir envoyé du sang de leurs malades et de nous avoir fourni les détails cliniques correspondants

TABLEAU II

Résultat des réactions sérologiques chez des malades atteints de 1 PCE avec pseudo ou phénomène L E positif — 2 LED (diagnostic bien établi) — 3 LED probable

DIAGNOSTIC	CAS	PHÉNOMÈNE L E			CONSOMMATION DE l'antiglobuline sur noyaux cell.		AGGLUTINATION DE PARTICULES DE LATEX					
							Acide désoxyribonucléique		Radioprotéine		Gamma-globuline	
		posit	pseudo	négat	posit	négat	posit	négat	posit	négat	posit	négat
PCE	o L W	+				—	+			—	—	
PCE	♂ N E	+				—		—		—	—	
PCE Felty	♀ M E	+			.+			—		—	+	
PCE	♀ D D	+				—		—		—		—
PCE	♀ M H		+			—		—		—	+	
PCE	♀ R T		+		1+			—		—	+	
PCE	o H N		+			—		—		—		—
PCE Felty	o J B		+		1+		+			—	+	
PCE	♀ A S		+			—	+			—	+	
PCE	♀ R D		+			—		—		—	+	
PCE	♀ M M		+			—		—		—	+	
PCE	♀ R.H		+			—		—		—	+	
PCE	♀ M.A		+			—	+			—	+	
PCE Felty												
Pancardite atteinte rénale	♀ M P	+			4+		+		+		+	
PCE	14 cas	5	9	0	4	10	5	9	1	13	12	2
LED	o A S			—	3+			—	+		+	
LED	o G Z	+			4+		+		+		+	
LED	♀ L B	+			3+		+		+			—
LED	♂ M G	+			4+		+		+			—
LED	♀ A.S	+			5+			—	+			—
LED	♂ A.A	+			4+		+		+			—
LED	♀ L.S	+			2+		+		+			—
LED	♀ P B		+		2+		+		+			—
LED	♀ M W	+			3+			—		—		—
LED	♀ 7480/A	+			3+		+		+			—
LED	♂ 7632/A	+			4+			—	+			—
LED	♀ 5139/A	+			3+			—	+			—
LED	♀ 7537/A	+			2+		+		+			—
LED	♂ 5163/A	+			3+		+		+			—
LED	♀ Los	+			4+			—		—		—
LED	♀ M B	+			3+		+			—	+	
LED	♀ C W	+			4+		+		+			—
LED	17 cas	15	1	0	17	0	11	6	14	3	3	14
LED prob	♀ R M		+		2+		+		+			—
LED prob	♀ M F			—	2+		+		+			—
LED prob	♀ M M		+			—		—		—	+	
LED prob	♂ K J		+		2+		+			—		—
LED prob	♀ R R		+		1+			—		—		—
LED prob	♀ A.L		+		2+			—		—	+	
LED prob	o J M		+			—	+		+			—
LED prob	7 cas	0	6	1	5	2	4	3	3	4	2	5

cutanées et en raison d une symptomatologie relativement pauvre Dans cinq de ces cas le test de consommation de l antiglobuline était positif mais deux fois l éluat ne consommait l antiglobuline qu a un seul titre Pour les autres tests voir tableau II

Dans deux cas de lupus erythémateux localisé il y avait une sérologie négative à l exception d un seul test MMM positif à l acide desoxyribo nucléique Avec le sérum d une malade atteinte de la « maladie a l apreso line » on notait une très forte consommation de l antiglobuline sur noyaux cellulaires

Sur les cinquante et un cas de polyarthrite chronique évolutive trente cinq (69 p 100) avaient un test positif avec la gammaglobuline Cinq fois, le phénomene L E a été trouve positif neuf fois on a note un pseudo phéno mène L E Le test de consommation de l antiglobuline sur noyaux a ete positif dans sept cas (14 p 100) dont cinq fois a un titre seulement et une fois a deux titres Une seule fois on a observé une forte consom mation de l antiglobuline de l ordre de celle qu on voit avec des sérums L E Le test à l acide desoxyribonucléique a été positif dans onze cas (11 p 100) *celui a la nucléoproteine dans deux cas* Les cas présentant un pseudo phénomene ou un phénomene L E positif sont reunis dans le tableau II

Sur quatre malades atteints de silicose et souffrant en outre d une arthropathie caractéristique d une polyarthrite chronique evolutive le facteur rhumatoide a été mis en évidence (syndrome de Kaplan) dans le serum des deux malades

Chez un malade atteint d une spondylarthrite la sérologie a été entiere ment négative Dans vingt cinq cas d arthropathies dégeneratives il y avai une fois un test positif à la gammaglobuline et une fois a l acide desoxy ribonucleique

Enfin le test a la gammaglobuline a été positif dans un cas sur vingt cinq affections diverses Dans ce groupe il y avait encore un pseudo phénomene L E et un test positif à l acide désoxyribonucleique

DISCUSSION

Nous voulons centrer la discussion des résultats sur le problème de la specificite du phénomene L E et sur la question de savoir s il est possible d établir des relations étroites entre le lupus érythémateux dissemine et la polyarthrite chronique evolutive

Parmi les 132 malades réunis dans ce travail 21 *presentaient un pheno mene L E typique* Dans ce groupe de vingt et un malades le diagno tic clinique de lupus érythémateux disseminé a pu etre établi chez seize indi vidus Dans quatre cas le diagnostic clinique etait celui d une polyarthrite chronique évolutive Le serum de quatre malades nous a ete envoyé par le Dr Irving A Friedman de Chicago Il s agit de cas dont le dia gnostic de polyarthrite chronique evolutive etait bien établi et dans lesquels on n a pu mettre en évidence aucune lesion tissulaire spécifique de lupus erythémateux disséminé et qui ont été décrits avec d autres cas par Friedman et coll dans les Ann Int Med (5) Le cinquieme cas est celui d une malade âgee de quarante et un ans et qui souffre depui l age de eize ans d une polyarthrite chronique évolutive avec évolution

vers un syndrome de Felty (splénomégalie leucopénie anémie avec moelle osseuse hypercellulaire) avec micropolyadénie et legere atteinte renale Une pancardite contractée en 1955 est un autre signe de la généralisation de cette affection A ce moment on a note un placard erythemateux sur le nez (Il s agit d une observation du Dr T Dorta de la Clinique medicale universitaire de Lausanne Dir Prof A Vannotti) Parmi ces cinq malades atteints de polyarthrite chronique évolutive avec phenomene L E positif, le test de consommation de l antiglobuline sur noyaux a éte positif deux fois dans le cas de M E (polyarthrite chronique evolutive avec syndrome de Felty) reaction positive a deux titres dans le cas de M P (cas de la Clinique medicale universitaire de Lausanne) réaction positive avec une consommation particulierement forte de l antiglobuline Le test au D N A a ete positif dans deux cas celui de la nucléoproteine dans un cas Le test a la gammaglobuline a été positif dans quatre de ces cinq cas D apres le tableau serologique seul le cas M P correspond a ce qu on observe avec le serum de malades atteints de lupus erythemateux disséminé Le cas M E est assez suspect d apres la sérologie de lupus érythémateux disséminé le cas C P est peu suspect et les autres ont entierement negatifs

Dans seize cas sur cent trente deux il y avait un pseudo phenomène L E positif caracterisé surtout par la présence de « Tartcells » c est a dire de phagocytes le plus souvent neutrophiles contenant des noyaux lymphocytaires non homogénéisés ou seulement peu homogenes et encore tres basophiles Dans ces pseudo phenomenes L E les altérations nucleaires intracellulaires si typiques pour le lupus érythémateux dissemine etaient absentes Dans six de ces cas il s agissait probablement d un lupus erythemateux dissemine dans un cas d une leucemie myéloide chronique et dans neuf cas de polyarthrite chronique évolutive La serologie de la leucemie myeloide chronique a ete entierement negative Les resultats des tests sérologiques des autres cas se trouvent dans le tableau II Nous attirons surtout l attention sur les cas de polyarthrite chronique évolutive avec phenomene pseudo L E positif Le test de consommation de l antiglobuline n a éte positif que deux fois et seulement avec une tres faible consommation de l antiglobuline Le test au DNA a été positif trois fois celui de la nucléoproteine dans aucun cas celui de la gammaglobuline dans huit cas sur neuf

Parmi les cinquante malades atteints de polyarthrite chronique evolutive quatorze ont donc presente un pseudo phenomene ou un phenomene L E positif Quelles conclusions pouvons nous tirer de cette constatation ? S agit il dans tous ces cas du meme phenomene qu on rencontre dans le lupus erythémateux disséminé typique ?

Le *test de consommation de l antiglobuline* nous permet une premiere distinction entre polyarthrite chronique évolutive et lupus erythemateux disséminé Tandis que ce test est positif dans tous les cas de lupus érythemateux dissémine typique et le plus souvent avec une très forte consommation de l antiglobuline il n a été positif que dans quatre cas sur quatorze et une seule fois avec une forte consommation

Dans trois autres cas de polyarthrite chronique evolutive sans pseudo phenomene L E il n y avait qu une faible consommation de l antiglobuline sur noyaux et à un titre seulement

Il y a deux possibilités pour expliquer ce fait ou bien il y a simplement

une difference d ordre quantitatif seulement le taux de l anticorps etant plus faible dans les cas de polyarthrite chronique évolutive ou bien il y a une difference d ordre qualitatif le facteur responsable du phenomene L E dans la polyarthrite chronique évolutive n étant pas identique à celui rencontré dans le sang de malades atteints de lupus érythemateux dissémine mais réagissant également avec des noyaux cellulaires (immuno réaction croisée)

Le résultat des autres reactions sérologiques plaide plutot en faveur de la seconde possibilite car le *test à la nucleoproteine* fortement specifique pour le lupus érythémateux disséminé et mettant en évidence le facteur L E n était positif que dans un seul cas de polyarthrite chronique évolutive avec pseudo phénomène ou phénomène L E positif, et ceci dans un serum qui présentait une tres forte consommation de l antiglobuline sur noyaux et qui provenait de la malade dont la symptomatologie clinique etait compatible avec le diagnostic de lupus érythémateux disséminé

Le test au DNA parait etre moins spécifique pour le lupus érythemateux disseminé (voir tableau I) Il a été positif dans cinq cas de polyarthrite chronique evolutive avec pseudo phénomene ou phénomene L E positif dans six autres cas de polyarthrite chronique évolutive dans un cas de lupus érythémateux localisé dans un autre d arthropathie dégénérative et enfin chez un malade atteint d une cirrhose hepatique

La comparaison de la fréquence du *facteur rhumatoide* dans les differents groupes donne également des renseignements intéressants Parmi les dix sept cas de lupus érythémateux disséminé il n a été trouvé que dans le serum de trois malades ce qui correspond à une fréquence de 18 p 100 Dans les cas de polyarthrite chronique évolutive il a été mis en evidence dans 69 p 100 des cas et dans le groupe de polyarthrite chronique évolutive avec pseudo phénomène ou phénomene L E le test était positif dans 86 p 100 Ce dernier groupe correspond donc a une forme de polyarthrite chronique évolutive qui est du point de vue sérologique particulierement active Si cette activite sérologique s accorde avec celle responsable du phénomene ou du pseudo phénomène L E de ce groupe elle contraste avec la faible activité des réactions sérologiques antinucléaires Dans le serum de malades atteints de lupus érythémateux disséminé la forte activite des réactions sérologiques antinucléaires va de pair avec une faible fréquence du facteur rhumatoide

De l ensemble de ces données il nous semble permis de deduire que le facteur L E responsable du phénomene L E dans les cas de polyarthrite chronique évolutive n est pas identique avec *le facteur L E du lupus* érythémateux disséminé il lui est très proche et il reagit également avec les noyaux cellulaires A son activité sérologique moins intense correspondrait l absence de signes tissulaires dans aucun des cas de Friedman et coll on n a pu mettre en evidence à l examen histologique, des organes des corps hematoxyliques specifiques pour le lupus érythemateux disséminé

Bien que le phénomene L E observe dans des cas de polyarthrite chronique évolutive ne semble pas etre sérologiquement identique a celui de lupus erythémateux disseminé l ensemble des réactions sérologiques indique cependant une parente entre ces deux affections D un coté le test a la gammaglobuline qui est positif dans environ 20 p 100 de lupus

érythémateux disséminé relie cette affection à la polyarthrite chronique évolutive de l'autre cote la fréquence des réactions nucleaires dans la polyarthrite chronique évolutive rapproche cette maladie du lupus érythémateux disséminé Le cas de M P pourrait etre le lien complet entre ces deux maladies car on y trouve associés une polyarthrite chronique evolutive et un *lupus erythémateux disseminé avec phénomene L E et sérologie* antinucléaire typique

En conclusion l'ensemble des reactions serologiques permet de differencier le groupe de malades atteints de polyarthrite chronique évolutive avec pseudo phenomene ou phénomene L E positif de celui de malades atteints de lupus érythémateux disséminé avec phenomene L E positif Cette différence se manifeste également par l'absence de corps hématoxyliques dans les tissus chez les malades atteints de polyarthrite chronique évolutive avec phénomene L E positif S'il a éte proposé a differentes reprises d'inclure ces cas particuliers de polyarthrite chronique évolutive dans le groupe de lupus erythémateux disséminé cette proposition a été faite en se basant sur la « spécificite morphologique absolue du phénomene L E[1] Mais comme toute expression morphologique le phénomène L E peut resulter de l'action de differents processus antinucléaires que seules des réactions sérologiques permettent de preciser

Si nous attribuons au phénomene L E dans les cas de polyarthrite chronique évolutive une autre genese que celle du phenomene L E dans le lupus erythémateux disseminé il s'agit dans les deux processus *de réactions antinucléaires* La distinction entre les deux phenomenes ne semble résider que dans de différents motifs antigéniques participant à la réaction le facteur L E du lupus réagirait spécifiquement avec la nucleoproteine et le facteur L E de polyarthrite chronique évolutive avec un autre motif nucléaire dont la nature exacte reste encore a preciser A cet égard il est permis de considerer le phénomene L E dans les deux affections comme un processus ayant une parenté étroite

Ainsi l'ensemble des réactions serologiques presentes dans le lupus erythémateux disséminé et la polyarthrite chronique évolutive relie les deux affections tout en laissant à chacune ses propriétes spécifiques

RÉSUMÉ

La decouverte recente du test cellulaire L E a considerablement facilite le diagnostic du lupus érythemateux disséminé (L E D)

A condition de donner a un certain nombre de criteres morphologiques l'attention qu'ils méritent on peut dire que ce phénomene possede un caractere spécifique tres nettement affirmé

Plusieurs de ces critères ne se rencontrent pas dans les phénomenes L E « faussement positifs » Etant moins spécifiques ils ont été groupés et nommés « phénomenes pseudo L E »

Le phénomene pseudo L E se *rencontre parfois dans* les cas de véritable lupus érythémateux disséminé mais il est généralement associé a d'autres manifestations pathologiques

Etant donné la spécificite marquee du phénomene L E véritable il y a lieu de signaler que ce même phénomene a été observé dans des cas isoles de rhumatisme articulaire déformant (R A D)

On ne peut considérer de tels cas comme de simples exemples de lupus erythémateux disséminé du fait de l absence des modifications histologiques caracteristiques du lupus érythémateux disséminé (corps hématoxyphiles)

Grâce aux tests serologiques mis au point au cours de ces dernieres annees (test de consommation d antiglobuline par les noyaux cellulaires test d agglutination de parcelles de latex avec l acide désoxyribonucléique avec la nucléo protéine et avec la gamma globuline) il a éte possible de progresser dans l etude de la nature de la reaction immunologique a laquelle ces phenomenes cellulaires particuliers peuvent etre imputés Par l emploi de tests serologiques effectués sur 132 sujets parmi lesquels se trouvaient 21 cas de rhumatisme articulaire deformant 17 cas de lupus erythemateux disséminé confirmés et 7 cas de lupus érythemateux disséminé probables il nous a été permis d etablir ce qui suit

Bien que du point de vue morphologique il ne soit pas possible de reconnaitre les phenomenes L E chez les sujets atteints de rhumatisme articulaire déformant et ceux atteints de lupus erythémateux disseminé on peut les distinguer l un de l autre a l aide des tests sérologiques

Dans les cas de lupus erythemateux disseminé les reactions sérologiques aux nucleo protéines ont presque toutes été positives (82 %) et le test de la consommation d antiglobuline a éte et cela tres nettement 100 % positif

Chez les sujets atteints de rhumatisme articulaire deformant et presentant un phénomène L E ou pseudo L E positif le test à la nucleo proteine a ete positif pour 7 % des cas et dans 28 5 % de ces serums le test de consommation d antiglobuline par les noyaux cellulaires a donne des resultats positifs *a titre tres faible*

Par ailleurs le test avec gamma globuline a presque toujours éte positif (86 %) pour le groupe de malades atteints de rhumatisme articulaire déformant et présentant un phénomene positif L E alors que dans le groupe de sujets atteints de lupus érythémateux on notait seulement 18 % de resultats positifs

Nous n avons rencontre qu un seul sujet classé dans le groupe des rhumatismes articulaires deformants pour lequel toutes les reactions spécifiques du lupus erythemateux aient été positives Jugé du point de vue clinique il doit s agir d un cas de rhumatisme articulaire déformant ancien avec developpement ulterieur de L E caractérise

Il semble probable que le phénomene de L E *authentique* aussi bien que le L E erythémateux associé aux rhumatismes articulaires déformants impliquent l un et l autre une reaction anti nucléaire mais se produisant selon le cas a des endroits differents du noyau cellulaire

Dans le lupus erythémateux visceral le point spécifique d attaque se trouve vraisemblablement situé dans la nucleo protéine alors que dans le cas de lupus érythemateux associé aux rhumatismes articulaires déformants il se localise probablement dans une partie qui n a pas encore éte exactement determinee du noyau cellulaire

A la lumiere de ces observations il est donc possible

— d une part d etablir une difference entre le phénomene L E que l on

rencontre associé aux rhumatismes articulaires déformants et le L E authentique

— d autre part qu il existe une relation étroite entre les deux maladies

SUMMARY

The introduction of the L E cell test has made it considerably easier to diagnose disseminated lupus erythematosus (LED) Provided that due attention is paid to a number of morphological criteria this phenomenon may be said to display a high specificity Several of these criteria are absent in so called false positive L E phenomena which — being less specific — have been grouped together under the term pseudo-L E phenomenon The pseudo L E phenomenon is occasionally observed in cases of LED but generally occurs in connection with other diseases

Having regard to the marked specificity of the full L E phenomenon it is noteworthy that this ame phenomenon has been encountered in isolated cases of rheumatoid arthritis (RA) Such cases cannot be regarded simply as examples of masked lupus erythematosus as the histological changes typical of lupus erythematosus (haematoxyphil bodies) are absent

With the help of serological tests elaborated in recent years (antiglobulin consumption test with cell nuclei latex particles agglutination test with desoxyribonucleic acid nucleoprotein and gamma globulin) it has been possible to gain further insight into the type of immunobiological reaction responsible for this particular cellular phenomenon From serological tests performed on 132 patients — including 21 cases of RA and 17 of confirmed and 7 of probable LED — the following facts have been established

Although the L E phenomena occuring in patients with RA and those with LED are morphologically indistinguishable they can be differentiated with the aid of serological tests Whereas in cases of LED the serologica reactions with nucleoprotein were almost always positive (82 p 100) and the antiglobulin consumption test with cell nuclei was invariably (100 p 100) positive and very markedly so in patients with RA showing positive L E or pseudo L E phenomena the nucleoprotein test was positive in only 7 p 100 of cases while in 28 5 p 100 of these serums the antiglobulin consumption test with cell nuclei yielded positive results with a very weak titre On the other hand the result of the gamma globulin test was almost always positive (86 p 100) in the RA group showing a positive L E phenomenon compared with positive results in only 18 p 100 of cases in the lupus erythematosus group Only in one patient assigned to the RA group were all the specific lupus erythematosus reactions strongly positive Judging from the clinical symptoms this was probably a long standing case of RA in which typical disseminated lupus erythematosus had developed later

It seems likely that the genuine L E phenomenon like the L E phenomenon associated with RA involves an anti nuclear reaction but with differing sites of attack in the cell nucleu In visceral lupus erythematosus the specific site of attack is probably located in the nucleoprotein whereas in the L E phenomenon occuring with RA its location is probably some part of the nucleus that has not yet been more closely defined

In the light of these findings it is thus possible on the one hand to differentiate between the L E phenomenon encountered in RA and the genuine L E phenomenon and on the other hand to recognise close connections existing between these two diseases

ZUSAMMENFASSUNG

Die Einfuhrung des L E Zelltestes machte es bedeutend leichter den Lupus erythematodes disseminatus (L E D) zu diagnostizieren Voraus gesetzt dass eine Reihe von morphologischen Kriterien beachtet werden besitzt dieses Phanomen hohe Spezifitat Mehrere dieser Kriterien fehlen *in den sogenannten falsch positiven L D Phanomenen die* — da wenig spezifisch — unter dem Ausdruck Pseudo L E Phanomene" zusammengefasst wurden Die Pseudo L E Phanomene konnen gelegentlich bei L LD Fallen beobachtet werden aber kommen gewohnlich in Verbindung mit anderen Krankheiten vor

Nachdem wir die hohe Spezifitat des vollen L E *Phanomens* heraus gestrichen haben ist es beachtenswert dass dieses gleiche Phanomen in *isolierten rheumatoiden Arthritisfallen (R A)* vorgefunden werden konnte Sochel alle konnen nicht als ein maskierter Lupus erythematodes betrachtet werden da die typischen histologischen Veranderungen des Lupus erythe matodes (haematoxiphile Korper) fehlen

Mit Hilfe der in den letzten Jahren ausgearbeiteten *serologischen* Tests (Antiglobulinkonsumptionstest mit Zellkernen Latexpartikel Agglutinationstest mit Desoxyribonucleinsaure Nucleoprotein und Gamma Globulin) war es moglich, weiteren Einblick in den Typ dieser immunobiologischen [illegible] Zellphanomen verantwortlich [illegible] Tests bei 13 Patienten [illegible] und 7 Falle wahrscheinlicher LED — gewonnen

Obwohl das bei Patienten mit RA und solchen mit LED vorkommende L E Phanomen morphologisch nicht zu unterscheiden ist so konnen diese Falle mit Hilfe serologischer Tests getrennt werden Wahrend bei LED Fallen die serologischen Reaktionen mit Nucleoprotein fast immer positiv (82 p 100) und der Antiglobulin Konsumptionstest mit Zellkernen bestandig (100 p 100) und sehr kraftig positiv waren so zeigten RA Patienten mit positivem L E — oder Pseudo L E — Phanomen in nur 7 p 100 der Falle einen positiven Nucleoproteintest wahrend in 28 5 p 100 dieser Seren der Antiglobulin Konsumptionstest mit Zellkernen positive Resultate mit sehr schwachen Titern ergab Andererseits war das Ergebnis des Gamma Globulintestes bei der ein positives L E Phanomen zeigenden RA Gruppe fast immer positiv (86 p 100) verglichen mit nur 18 p 100 positiven Resultaten bei der Lupus erythematodes Gruppe Nur bei einem zur RA Gruppe gerechneten Patienten ware *nall spezifischen Lupus erythematodes* Reaktionen stark positiv Wenn man nach den klinischen Symptomen urteilt so war dies wahrscheinlich *ein protrahierter* R A F all in dem sich spater ein typischer Lupus erythematodes disseminatus ausbildete

Es scheint dass das genuine *L E Phanomen* ahnlich dem mit RA verbundenen L E *Phanomen* ein anti nukleare Reaktion beinhaltet

aber mit unterschiedlichen Angriffspunkten im Zellkern Beim visceralen Lupus erythematodes ist der spezifische Angriffspunkt wahrscheinlich im Nucleoprotein lokalisiert wahrend der Angriffspunkt beim L E Phanomen bei RA in einer noch naher zu bestimmenden Kernpartie liegt

Unter den Gesichtspunkten dieser Resultate ist es einerseits also moglich zwischen dem bei RA vorkommenden L E Phanomen und dem genuinen L E Phanomen zu unterscheiden und andererseits enge Beziehungen zwischen diesen beiden Krankheiten zu beachten

RESUMEN

El test celular LE ha facilitado considerablemente el diagnóstico del lupus eritematoso diseminado (LED) Puede decirse que este fenomeno presenta una gran especificidad si se tienen en cuenta las necesarias pre cauciones El llamado falso positivo LE menos especifico ocurre general mente en otras enfermedades aunque ocasionalmente se lo encuentra tam bién en el LED

El hecho de que el test positivo haya sido obtenido en algunos casos de artritis reumatoidea (RA) es de gran significación dada su especificidad Esos casos no pueden ser considerados como lupus eritematoso enmascarado pues en ellos no se han encontrado las tipicos modificaciones histologicas (cuerpos hematoxifilos)

Un conocimiento más profundo de la reaccion inmunobiológica respon sable ha sido aportado por los test serologicos recientes test antiglobulinico con los nucleos celulares aglutinación de particulas de latex con ácido desoxirribonucleico nucleoproteina y gama globulinas Los resultados obtenidos en 132 pacientes incluyendo 21 casos de RA 17 de LED confir mado y 7 de LED probable autorizan las siguientes conclusiones

Aunque el test celular LE presentado por pacientes con RA es el mismo que presentan los que tienen LED se puede establecer una diferenciacion mediante las reacciones serológicas Asi mientras en los casos de LED las reacciones con nucleoproteinas son casi siempre positivas (82 p 100) y el test antiglobulinico invariablemente positivo (100 p 100) los pacientes de RA con test positivo LE solo dan una incidencia de 7 p 100 y 28 5 p 100 respectivamente Por otra parte los resultados con gamaglobulina son generalmente positivos (86 p 100) en los casos de RA y solamente en 18 p 100 de los casos de LED Solamente en un caso un paciente del grupo RA con test LE positivo presentó las reacciones especificas del LED y a juzgar por el cuadro clinico sin duda se trataba de un paciente con una RA muy vieja y en el cual el LED se habia instalado ulteriormente

Parece probable que el fenómeno LE como asimismo el fenomeno LE asociado con RA involucre una reaccion antinuclear pero en distintos lugares del nucleo celular En el lupus eritematoso visceral el sitio específico de ataque está probablemente en la nucleoproteina mientras que en el fenómeno LE asociado a RA reside en otra zona del nucleo no bien definida por ahora

De todas estas investigaciones resulta posible actualmente la diferencia ción entre el fenómeno LE encontrado en RA y el fenómeno LE genuino asi como la comprensión de los puntos de contacto que existen entre estas dos enfermedades

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DISCUSSION

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Ayant reussi a demontrer que l acide desoxyribonucleique (D N A) est l un des constituants leucocytaires réagissant avec les leucoprecipitines décelées dans le serum de malades atteints de lupus erythemateux dissemine (L E D) nous avons etudie la reaction que ces sérums donnent avec le D N A par deux méthodes precipitation (ring test double diffusion en milieu gelifié immuno electrophorese) et fixation du complément Nous avons abandonne la technique de l hémagglutination passive qui s est averée peu satisfaisante pour l etude de cette reaction malgre une absorption préalable soigneuse sur hematies de mouton les sérums de L E D entrainent souvent une agglutination de hematies tannées mais non sensibilisées de plus les resultats positifs avec hématies sensibilisees ne sont pas parfaitement reproductibles Nous n avons pas utilise la technique d agglutination des particules de latex

La substance des serums de L E D qui reagit avec le D N A n est pas une histone elle n est pas précipitee par le reactif de Mirsky le précipité qu elle forme avec le D N A n est pas totalement redissout par NaCl 1 ou 2M et le rapport ponderal proteines/D N A dans ce precipité est beaucoup plus elevé que dans les nucléohistones Cette substance a des propriétes analogues à celle d un anticorps elle fixe le complément lors qu elle réagit avec le D N A elle est electivement precipitée par un immun sérum anti γ globulines on peut l extraire du precipite spécifique lavé en le traitant par des solutions salines concentrées ou par la desoxyribo nucléase et on constate alors qu elle possède la spécificité antigénique des γ globulines C est bien avec le D N A que réagit cet anticorps L hypothese d une impureté peut etre rejetée la reaction est positive avec de minimes quantités de D N A (tant a l épreuve ring te t et en immuno électrophorèse que par la fixation du complement) et elle devient négative apres action de la désoxyribonucléase Cet anticorps ne reagit pas avec l acide ribonucléique mais réagit avec des D N A d origine tres diverse humaine animale ou bactérienne il ne s agit pas de reactions croisees Il est donc logique de penser que cet anticorps reagit avec une partie de la molécule de D N A ayant une structure analogue dans tous les D N A

Cet anticorps réagit encore avec du D N A dépolymerisé par les ultrasons mais ne réagit plus (ni précipitation, ni fixation du complément ni surtout inhibition) avec le D N A dépolymérisé par la désoxyribonucléase Or les deux chaines du modele de structure de Watson et Crick se séparent sous l action de cet enzyme mais ne semble pas se séparer sous l action des ultrasons On peut donc imaginer que l anticorps réagit avec un ensemble de groupements situés sur les deux chaines a des distances réciproques déterminées

Les rapports entre les anticorps anti nucleaires des sérums de L E D et le phenomene L E ne sont pas encore totalement élucidés Avec Robineaux nous avons constaté que les anticorps anti D N A isolés a partir du precipité specifique sont capables d induire un phenomene L E typique si on les met en presence de leucocytes normaux et de sérum normal frais Mais nous n avons pas reussi à déceler des anticorps anti D N A dans certains serums de L E D donnant un phénomène L E de plus les surnageants obtenus apres épuisement des anticorps précipitants anti D N A se sont toujours averés capables d induire le phenomene L E meme si l on se place dans la zone d excés d antigene là ou d eventuels anticorps non précipitants devraient etre neutralisés Ces faits joints aux données des autres auteurs (impossibilite de provoquer le phenomene L E apres absorption sur noyaux ou sur nucléo protéines de toutes origines persistance du phénomène L E apres absorption sur nucleoprotéine traitee par la désoxyribonucléase) nous ont conduit à émettre les deux hypotheses suivantes *a*) différentes variétés d anticorps anti noyaux de spécificite differente seraient capables d induire le phénomène L E anticorps anti D N A et anticorps anti protéine ou peut être plutot anticorps reagissant avec un groupement situé à la jonction D N A proteine *b*) si seuls les anticorps anti D N A produisent le phénomène L E il faudrait admettre que des complexes solubles anticorps D N A soient capables en se dissociant au contact de la cellule de donner le phenomene L E

Dans quelle mesure ces reactions serologiques auront elles un interet clinique et permettront elles d élucider le problème des cellules L E authentiques observées dans d autres circonstances que le L E D ? On ne peut encore se faire une opinion dans ce domaine Dans un assez grand nombre de serums provenant de malades atteints avec certitude de L E D nous n avons pas pu déceler d anticorps anti D N A (Tableau I) Mais dans tous ces cas, sauf un il s agissait de malades soumis depuis plusieurs semaines ou mois a la corticothérapie et tres améliorés Par contre nous n avons jamais encore observe de reactions positives en dehors du L E D nous avons en particulier examiné 23 sérums de polyarthrite chronique évolutive dont 2 donnaient un phenomène L E Mais le nombre de malades étudies est trop faible pour que l on puisse se permettre une quelconque conclusion A notre avis les donnees sérologiques rapportees par Miescher ne plaident pas de façon formelle en faveur de l existence au cours de la polyarthrite évolutive d anticorps anti nucléaires capables de donner le phenomene L E et possédant une spécification distincte de celle du ou des facteurs L E du L E D De plus dans le tableau II du rapport de Miescher on note certaines discordances encore difficiles à expliquer dans l état actuel de nos connaissances *a*) pour certains sérums donnant le phénomene L E la consommation d anti globuline sur noyaux ainsi que

l agglutination des particules de latex avec nucléo protéines sont négatives alors que ce dernier test est positif quand on utilise le D N A b) avec un sérum ne donnant pas le phenomene L E les trois réactions sérologiques (consommation d anti globuline sur noyaux agglutination des particules de latex avec nucléo protéines et avec D N A) sont positives c) certains serums avec phénomène L E et forte consommation de l anti globuline sur noyaux donnent des reactions négatives tant avec les nucleo proteines qu avec le D N A Si la presence d anticorps anti nucleaires dans le serum de certains malades peut etre tenue pour demontree l analyse de ces reactions sérologiques en est à ses tout premiers pas et les resultats doivent encore en etre interpretés avec circonspection Il est possible que l aspect morphologique du phenomene L E puisse etre realisé par des mecanismes differents Une triple enquete devrait etre menee dans toutes les circonstances ou l on constate une nucleo phagocytose etude dynamique du phénomene L E telle que la pratique Robineaux étude cytochimique analogue a celle que Godeman a menee dans le L E D étude sérologique Il nous semble que la nucléo phagocytose provoquee par les immunsérums anti leucocytes ou anti noyaux soit differente de celle du phenomène L E dans aucun de nos immunserums anti leucocytaires nous n avons pu déceler la presence d anticorps anti D N A Nous entreprenons actuellement l etude d immunsérums anti D N A

Les references bibliographiques et l iconographie seront trouvees dans M Seligmann Etudes immunologiques sur le lupus erythémateux disseminé *Rev Franç Etudes Clin Biol* 3 558 584 1958

TABLEAU I

SÉRUMS DE	NOMBRE	ANTICORPS ANTI D N A			
		PRÉCIPITATION		FIX COMPLEMENT	
		+	—	+	—
Lupus Erythémateux Disséminé	47	26	21	28	19
Id non ou peu traités	16	15	1	15	1
Lupus chronique	4	0	4	0	4
Polyarthrite chronique évolutive	23	0	23	0	23
Myélome	7	0	7	0	7
Macroglobulinémie	5	0	5	0	5
Divers	90	0	90	0	90
Sujets normaux	100	0	100	0	100

IMMUNOLOGIE DES HOMOGREFFES (*)

par

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Avant d aborder l étude de phénomenes assez complexes il semble utile de rappeler quelques points de terminologie

On designe sous le terme d *homogreffe* la greffe d un fragment de tissu ou d organe provenant d un individu *(donneur)* sur un individu *(receveur)* de la meme espèce Ceci distingue l homogreffe de l *autogreffe* ou donneur et receveur constituent un seul et meme individu et de l *héterogreffe* ou donneur et receveur sont d espèce differente On reserve le nom d *isogreffes* aux cas ou donneur et receveur appartiennent tous deux a une meme souche extremement pure (le terme de syngénésiogreffe est utilisé dans un sens proche mais moins strict) On utilise le terme de *transplantation* (auto homo et hétéro transplantation) lorsqu il s agit de la greffe d un organe entier (rein par exemple) avec rétablissement de continuite des vaisseaux et des conduits (excréteurs par exemple) On parle de greffon ou de trans plant pour designer la partie greffee ou transplantée Le terme de greffe bréphoplastique est réserve aux cas ou le greffon provient d un embryon ou d un nouveau né (R M May) (1) Quant a la greffe de tissus cancereux nous ne l envisagerons qu incidemment car elle presente des particularites qui la font sortir du cadre du sujet

I EXPOSÉ PRÉLIMINAIRE ET INTERPRÉTATION DES FAITS ESSENTIELS

A Exposé préliminaire des faits essentiels

Dans le cas le plus simple celui d une greffe de peau chez le lapin par exemple on peut suivre l évolution du greffon jour apres jour par l obser

( ) Travail réalisé avec l aide de la Hel n Hay Wh tney Foundation
( ) Raoul Kourilsky directeur

vation macroscopique, l'etude microcapillaroscopique (2) et l'histologie par biopsie (3)

Si l'on compare l'evolution d'une homogreffe à celle d'une autogreffe (3 4 5) on est frappé par la similitude d'evolution des deux pendant plusieurs jours Le greffon est d'abord assez pâle puis un petit piquete vasculaire apparait vers le 3e 4e jour lui donnant une coloration rosée Ceci provient de l'etablissement de *néocapillaires* croissant à partir du lit du greffon et etablissant une connexion vasculaire entre le greffon et le receveur L'epithélium malpighien est vers le 6e jour siege d'une intense activite mitotique s'accompagnant d'une legere desquamation Mais à partir du 7e 8e *jour environ l'evolution du greffon va devenir tres differente suivant* qu'il s'agit d'une autogreffe ou d'une homogreffe Dans le premier cas en effet l'évolution se poursuit vers le retour à un aspect normal de la peau greffee aspect qui est atteint en 2 a 3 semaines alors que dans le cas de l'homogreffe on voit le greffon devenir cyanotique l'épithelium desquamer abondamment laissant apparaitre une surface suintante des indurations brunatres se former allant bientot jusqu'à la necrose complete et totale du greffon qui se trouve finalement rejeté

Correlativement les vaisseaux du greffon se sont entourés d'un manchon de cellules a noyaux ronds (lymphocytes et histiocytes) et se sont progressivement thromboses L'epithelium malpighien continuant a desquamer a cesse de proliférer L'évolution totale a duré 8 à 12 jours suivant la technique utilisee la taille du greffon et certaines variations individuelles

B Interpretation des faits Les théories proposées

Sans entrer dans le detail des theories qui ont eté proposées pour interpreter l'echec constant (sauf quelques exceptions trompeuses pour la plupart) des homogreffes il nous a semble logique de les grouper sous deux rubriques (5) suivant le mecanisme qu'elles invoquent les théories de l'elimination passive et celles du rejet actif

Théories de l'élimination passive

D'apres ces theories le greffon ne trouvant pas chez le receveur les substances necessaires à sa survie mourrait d'inanition pour *ainsi dire* Cette *theorie de l'athrepsie* émise il y a longtemps par Ehrlich (6) a éte renouvelee par Conway et coll (7) qui ont cru pouvoir dire que les homogreffons *ne se vascularisaient pas*

En fait les homogreffons etudies par ces auteurs etaient placés dans des conditions antiphysiologiques et nous avons vu qu'un homogreffon normal se vascularise apres avoir survécu par imbibition pendant plusieurs jours (2 3 4 5 8) D'ailleurs un homogreffon peut *survivre tres longtemps* sans vascularisation dans la chambre anterieure de l'œil par exemple (9) ou dans une chambre poreuse artificielle telle celle realisee par Algire (10) et qui plus est s'il arrive que ce greffon devienne vascularisé alors il mourra en quelques jours Si bien que la mort du greffon n'est pas due a l'absence de vascularisation mais est, au contraire en rapport direct avec cette vascularisation Le greffon ne meurt pas « passivement » il est activement rejete par le receveur

THÉORIES DU REJET ACTIF

Ce sont donc les seules théories à prendre en considération non pas seulement *la théorie de la réaction cellulaire locale* défendue par J Loeb (11) et Murphy (12) et encombrée de concepts quasi métaphysiques suivant lesquels le greffon serait rejeté par l'action locale des cellules lymphocytaires environnantes attirées par quelques facteurs « différentiels » existant dans le greffon non plus que la *théorie des groupes tissulaires* (qui serait un analogue des groupes sanguins) infirmée par le fait que de tels groupes ont été recherchés et non retrouvés (13) et par le fait qu'en culture de tissu les cellules d'un individu croissent parfaitement en présence de n'importe quel sérum homologue mais surtout la *théorie de l'immunité activement acquise* la seule qui réunisse actuellement assez de preuves pour ne plus pouvoir être réfutée C'est son étude qui doit constituer l'essentiel de ce rapport

II ARGUMENTS PLAIDANT EN FAVEUR DE LA THÉORIE DE L'IMMUNITÉ ACTIVEMENT ACQUISE

On peut en une seule phrase synthétiser la signification de chacun de ces arguments

Tout facteur qui joue un rôle d'ordre immunologique dans le domaine du receveur dans celui du greffon ou bien qui joue un rôle dans les rapports immunologiques existant entre receveur et greffon agira sur le temps de survie du greffon Cette intervention se fera dans le sens que permet de prévoir la théorie de l'immunité activement acquise

En effet

1° *Tout facteur augmentant les réactions immunologiques du receveur vis à vis du greffon écourtera le temps de survie de ce dernier*

Le meilleur exemple en est fourni par le phénomène du « second set » décrit par Medawar (3 14) un second greffon d'un même donneur à un même receveur meurt plus vite que le premier Des greffons successifs du même donneur au même receveur finiront même par ne plus recevoir aucune vascularisation c'est le phénomène de la « greffe blanche » décrit par Rapaport et Converse (15) indice d'une immunisation intense

2° *Tout facteur diminuant les réactions immunologiques du receveur augmentera le temps de survie du greffon*

Parmi les moyens utilisés il en est deux surtout l'irradiation X et l'hormonothérapie (A C T H et cortisone) Ces deux procédés sont connus comme inhibiteurs (au moins partiels) des réactions immunitaires (16) Ils entraînent également un prolongement appréciable du temps de survie du greffon (17)

3° D'ailleurs *un receveur ne rejettera un greffon que si une réaction immunologique peut prendre place entre greffon et receveur*

Ceci suppose que le receveur est « immunologiquement compétent » (expression employée par Mitchison (131) que le greffon est suffisamment antigénique qu'il existe des différences d'ordre immunologique suffisantes entre greffon et donneur et enfin dans le cas particulier des réactions ici

mises en jeu que des connexions vasculaires s établissent entre greffon et receveur Examinons successivement ces differents points

Compétence immunologique du receveur — Le rejet du greffon ne prendra pas place si le receveur est incapable d une reaction immunologique C est le cas pour d assez nombreux Invertébrés chez lesquels manquent les systèmes cellulaires responsables des reponses immunologiques en particulier les plasmocytes (19) Ce que l on observe ici au bas de l echelle phylogénique on l observe egalement au début de l evolution ontogenique C est ainsi que l on peut pratiquer avec succès des greffes (et meme des héterogreffes) (20) chez l embryon de poulet ou encore des homogreffes de peau chez la souris ou le rat nouveau nes

Antigenicité du greffon — Elle aussi est necessaire au rejet du greffon

Le cas le plus net est celui des greffes embryonnaires ou brephoplastiques (R M May) (21) ou le greffon embryonnaire, encore peu differencie est faiblement antigenique ce qui permet de longues survies aux homogreffons La peau elle meme peut etre greffee avec succes dans des conditions semblables (22)

Differences d ordre immunologique entre greffon et receveur — Ce dernier point est tellement vrai que lorsqu il n existe pas de difference antigenique (jumeaux homozygotes) l homogreffe se comporte exactement comme une autogreffe et persiste indéfiniment Par ailleurs entre des animaux de souche pure [souris par exemple (23) ou cobayes (24)] l homogreffon a une survie d autant plus longue que la purete génétique de la souche est plus grande (c est à dire tend plus vers l homozygotie totale)

Chez l homme de même Rogers (25) a pu montrer que le temps d survie d un greffon cutane va de 8 jours à une survie permanente avec des durees de plus en plus prolongees suivant que donneur et receveur sont non relies et de groupes sanguins différents non reliés mais de groupes sanguins (meme les mineurs) strictement semblables relies de pres (syngé nesiotransplantation) jumeaux dizygotes ou enfin jumeaux homozygotes ou la survie est définitive de meme que dans les isogreffes pratiquées entre animaux d une souche genetiquement tres pure (23 24)

Nécessite de connexions vasculaires entre greffon et receveur — Enfin la reaction immunologique du receveur envers le greffon ne semble pouvoir prendre place que si des connexions vasculaires sont etablies entre eux. Alors que des connexions vasculaires sanguines (c est à dire un apport san [illegible] de la greffe par le receveur — même sensi [illegible] ues sont suffisantes [illegible] eveur vis a vis du donneur, comme il ressort d une tres elegante etude de Medawar (9) Ces faits comme nous le verrons ont une grande portée theorique

Tel est l ensemble des faits qui plaident en faveur de la theorie suivant laquelle le rejet de l homogreffon est du a une reaction d immunite activement acquise Cependant les objections n ont pas manque

III OBJECTIONS A LA THÉORIE DE L IMMUNITÉ ACQUISE

Ces objections peuvent se grouper sous cinq rubriques

— aucun des arguments precedents n est absolument contraignant

— il existe des cas d homogreffes qui prennent

— on ne trouve pas de témoins d hypersensibilisation du receveur vis a vis du greffon

— on ne trouve pas chez le receveur d anticorps anti greffon

— d autres theories peuvent expliquer les phénomenes observés

Si l on considere de pres ces objections on s aperçoit qu elles sont basees sur des exceptions mal interpretees ou bien qu elles pourraient également s appliquer a des phenomènes dont la nature immunologique est absolument incontestable

Examinons les donc successivement

1° Aucun des arguments précédents n est absolument contraignant

Cela est vrai si l on considère isolément chacun des faits que nous venons de relater mais il faut bien reconnaitre que ces faits se groupent en un faisceau d arguments logiques qui tous convergent pour etayer la theorie de l immunité acquise

2° Il existe des cas d homogreffes qui prennent

Ceci est du point de vue biologique rarement vrai En effet des succes pratiques comme les greffes artérielles ou osseuses constituent en fait des echecs biologiques car les cellules vivantes de ces transplants meurent et les transplants ne servant que de support sont réhabités par les cellules du receveur La meilleure preuve en est que les transplants artériels ou osseux conserves morts donnent lieu a des reussites pratiques souvent supérieures Ces greffes peuvent d ailleurs etre remplacées par des protheses en matiere plastique

La greffe de cornee constitue un cas particulier ou l on peut encore se demander si le greffon est véritablement vivant (au sens de capable de synthetiser des protéines) De toute maniere meme s il est vivant du fait qu il n est pas vascularise sa survie ne constitue en aucun cas une objection valable Il est enfin un certain nombre de cas (bien inferieur au nombre de cas rapportes) ou une homogreffe de peau prend veritablement et de manière durable en dehors du cas d homozygotie Comme il s agit en règle de greffes de parents a enfant et que ces cas correspondent a une probabilité extremement minime on est en droit de supposer que la constitution *genetique des deux parents etait tres proche et qu en consequence* le patrimoine génetique (et donc antigenique) de l enfant ne differait pas sensiblement de celui des parents qui a donne le greffon Ou bien peut etre le receveur présentait il une alteration de ses réactions immunitaires du type de celles qui sont rencontrees chez les sujets agammaglobulinemiques (26)

3° On ne trouve pas de témoins d hypersensibilisation du receveur vis a vis du greffon

Cette objection ne peut d ailleurs etre formulee que si l on ne tient pas le phénomène du *second set* comme un temoin d hypersensibilite Par

ailleurs de tels tests (cutanés par exemple) n'ont été que rarement recherchés. Nous les avons recherchés (Voisin et Maurer, 27, 28) chez des lapins et des cobayes soumis à des homogreffes cutanées et nous nous sommes trouvés en présence de l'obstacle suivant : l'extrait de tissu utilisé comme « antigène » test est par lui-même fortement pro-inflammatoire et donne lieu à des réactions non spécifiques. Ce qui ne permet pas de conclure dans un sens ni dans l'autre. Mais nous verrons pourquoi le phénomène du *second set* constitue bien un témoin de cette hypersensibilisation spécifique.

4° ON NE TROUVE PAS CHEZ LE RECEVEUR D'ANTICORPS ANTI-GREFFON. Ceci est souvent exact. Les techniques utilisées en immunologie classique ne réussissent pas à mettre en évidence dans le sérum du receveur des anticorps anti-greffon. Utilisant des tests tels que le test de précipitation interfacial, le test très sensible d'anaphylaxie cutanée passive suivant *la technique d'Ovary, le test d'anaphylaxie générale active*, nous n'avons pas réussi à trouver trace de tels anticorps (Voisin et Maurer, 27, 28). En revanche, au cours d'expériences de transfert passif de l'hypersensibilité au greffon, il nous a paru que, dans quelques cas au moins, il existait assez d'anticorps circulants anti-greffon pour accélérer la mortification d'un greffon du même donneur placé sur un autre receveur (Voisin et Maurer, 28). Par ailleurs, P. Gorer, au cours d'études portant surtout sur des homogreffes de tissu cancéreux (29) mais aussi de tissu cutané (30), a démontré l'existence d'anticorps spécifiques hémagglutinants et cytotoxiques « in vitro » pour les cellules tumorales. De même, mais travaillant sur des cellules épithéliales cutanées de lapin, Billingham a montré qu'après avoir été mises en présence de sérum de lapins immunisés (par greffe de peau) *contre l'animal fournisseur de ces cellules, elles étaient incapables*, une fois retransplantées sur le donneur dont elles provenaient, de se développer en une lame épithéliale. Ce phénomène d'inhibition ne se produit évidemment pas si les cellules épithéliales sont mises en présence d'un autre sérum de lapin non préparé (31). Enfin, au cours de travaux qui demandent encore confirmation, Bollag aurait réussi à mettre en évidence de tels anticorps anti-greffon par une méthode néphélométrique (32).

En dehors même de ces résultats positifs, l'objection précédente n'est pas rédhibitoire car on connaît de nombreux cas d'hypersensibilité spécifique (au sens immunologique) sans anticorps circulants décelables, qu'il s'agisse de cas d'hypersensibilité atopique (cas de plus en plus rares maintenant) ou surtout d'hypersensibilité de type retardé dont le prototype est *l'hypersensibilité tuberculinique, où l'on ne retrouve* aucun anticorps *circulant* anti-tuberculoprotéine et que le sérum d'un sujet *hypersensible est* incapable de transmettre passivement à un sujet normal. Nous aurons d'ailleurs l'occasion d'analyser plus longuement le rôle du sérum *et la* signification de ce rôle dans le rejet des homogreffes.

5° D'AUTRES THÉORIES PEUVENT EXPLIQUER LES PHÉNOMÈNES OBSERVÉS. Ici encore on ne peut arriver à faire une telle objection que si l'on considère isolément chacun des phénomènes observés. Mais si on les considère tous, y compris les exceptions, on ne peut fournir d'interprétation d'ensemble satisfaisante en dehors de la théorie de l'immunité acquise.

D'ailleurs cette théorie reconnaît aujourd'hui les preuves encore plus formelles contre lesquelles les objections précédentes ne peuvent plus tenir.

IV. PREUVES FORMELLES DU BIEN FONDÉ DE LA THÉORIE DE L'IMMUNITÉ ACQUISE

La preuve formelle du bien fondé de la théorie de l'immunité acquise comme cause du rejet des homogreffes est apportée par un ensemble d'expériences dont on peut résumer la signification générale en disant que *l'on peut à volonté écourter ou prolonger (voire indéfiniment) la survie d'une homogreffe en agissant sur l'hypersensibilité du receveur vis-à-vis du greffon et que cette hypersensibilité est strictement spécifique au sens immunologique du terme.*

A. Raccourcissement du temps de survie par hypersensibilisation spécifique

Ce raccourcissement peut s'obtenir, nous l'avons vu, par l'application du phénomène du *second set* (mort accélérée d'un deuxième greffon). Or il s'agit bien là d'un phénomène d'hypersensibilité spécifique que l'on peut par ailleurs reproduire « artificiellement » par des moyens purement immunologiques.

1. *Second set, phénomène d'hypersensibilité spécifique.*

Ainsi que l'a démontré Medawar (3, 14) la mort accélérée d'un deuxième greffon ne s'observe que s'il provient d'un même donneur. Le premier greffon peut d'ailleurs être remplacé par une injection de leucocytes. Bien plus (Dempster) (33) une greffe de rein sensibilise le receveur non pas à une seconde greffe de rein d'un autre donneur mais à une seconde greffe en provenance du même donneur. Cette seconde greffe peut être de rein ou de peau. De même une première greffe de peau sensibilise le receveur non pas à une seconde greffe de peau d'un autre donneur mais à une seconde greffe (peau ou rein) en provenance du même donneur. Rein et rate peuvent également être utilisés indifféremment pour sensibiliser le receveur à un certain donneur (Simonsen) (34). Si bien que l'hypersensibilité à laquelle donne n[illegible]

du même donneur au même receveur sera rejeté encore plus vite (35) et que des greffons ultérieurs finiront par ne plus être vascularisés (15). Enfin nous avons fréquemment observé deux à trois jours après une deuxième greffe d'un même donneur à un même receveur une réaction inflammatoire importante de la peau du receveur autour du greffon (28) et Rapaport et Converse (36) ont remarqué chez des hommes recevant une 2ᵉ, 3ᵉ ou 4ᵉ greffe de peau d'un même donneur une intense réaction inflammatoire « de rappel » au niveau des anciens sites de greffes (déjà éliminées) au moment de la réaction aboutissant au rejet de la greffe présente. Ceci ne s'observant pas si la greffe présente provient d'un autre donneur. Tous ces faits montrent le caractère spécifique (au sens immunologique) des phénomènes observés au cours de l'évolution d'une greffe de *second set*. Les expériences suivantes apportent une certitude de plus.

2 *Reproduction artificielle du phénomène du second set par des moyens purement immunologiques*

Il est en effet possible de reproduire un phenomene du *second set* « artificiellement » c est a dire sans faire de premiere greffe mais en sensibilisant le receveur vis à vis du donneur par les moyens classiques en immunologie de sensibilisation active ou passive

Sensibilisation active — Une mort accelerée d un greffon de peau comparable en tous points à un phenomene du *second set* s observe chez des lapins prealablement soumis à des injections d un broyat de peau du futur donneur mélange à des substances adjuvantes (Voisin et Maurer 27, 28) Lorsque la sensibilisation est suffisamment intense on peut meme provoquer le phenomene de la greffe blanche (Voisin et Maurer 37)

Sensibilisation passive — Une mort acceleree du greffon s observe egalement si l on injecte chez le receveur un antiserum anti donneur prépare chez un animal d espece differente (lapin pour des homogreffes de cobayes) (Voisin et Maurer 27 28) Dans ce dernier cas les anticorps présents dans l antiserum sont tres puissants car diriges non seulement contre le donneur mais contre tous les animaux de son espece D ou les phenomenes suivants frequence de la greffe blanche mortification accelerée d une homogreffe de peau provenant d un autre donneur mortification meme d une autogreffe et finalement possibilité d une action fatale chez l animal *receveur de serum Si cherchant a accelerer* la mort d un greffon de peau on injecte a un animal qui vient de recevoir une greffe de peau du serum provenant d autres animaux de meme espece préalablement soumis a des greffes de peau du meme donneur il semble que l on puisse parfois obtenir une accéleration effective du rejet du greffon (27 28)

Le phenomene du *second set* est donc bien un phenomene de nature immunologique puisque c est un phenomène strictement specifique et qu on peut le reproduire par des moyens purement immunologiques

Mais si l on peut en provoquant une hypersensibilite specifique ecourter la survie d un greffon il serait certainement aussi probant et encore plus spectaculaire de reussir a prolonger cette survie au moyen d une desensibilisation specifique Cela est également realisable

B Prolongation du temps de survie du greffon par désensibilisation spécifique

On peut en effet prolonger la survie d une homogreffe chez un animal par desensibilisation temporaire precedant immediatement la greffe ou bien obtenir une survie definitive par desensibilisation pratiquée chez le receveur au moment de sa vie embryonnaire Dans les deux cas cette desensibilisation est specifique du donneur dans les deux cas également le terme désensibilisation ne prejuge pas du mecanisme immunologique intime qui conduit à cet etat « réfractaire »

1 *Prolongation du temps de survie du greffon par désensibilisation temporaire*

Billingham et Sparrow (31 38) ont montre que l on peut doubler au moins le temps de survie d une homogreffe de peau en faisant au futur receveur (22 et 10 jours avant la greffe) deux injections intraveineuses d une suspension de cellules (epitheliales malpighiennes ou leucocytaires) du futur

donneur Quel que soit le mecanisme intime de ce phenomene il est specifique du donneur

2 *Survie indéfinie des greffes chez des animaux desensibilises pendant leur vie embryonnaire*

artificiellement un tel etat de *tolerance specifique acquise* (nom dont ils ont baptise eux memes ce phenomène) Le schema de leur experience est le suivant ils injectent a un embryon de souris blanche des cellules sanguines de souris noire Lorsque le souriceau blanc est ne et devenu adulte ces auteurs lui font une greffe de peau de souris noire (souche d une haute pureté genetique ce qui permet d avoir recours pour le greffon a une autre souris qu a la souris donneuse de cellules) Cette greffe de peau noire est alors capable de survivre indéfiniment (dans le cas de tolerance complete) Une telle tolerance specifique acquise peut egalement etre obtenue chez certaines especes par injection de cellules chez des animaux nouveau nes (Woodruff 42) Enfin une tolerance partielle a des hetero greffes (entre especes differentes) a pu etre obtenue recemment par la meme méthode (Hašek 43 44 Egdahl et Varco 45)

Ce phenomene de tolerance spécifique acquise est comparable au phenomène d inhibition specifique qu ont etabli maintenant les immunologistes (46 47 48 49) a savoir que l injection d un antigene a dose suffisante (50) a un animal durant sa vie intra embryonnaire (ou meme neo natale) entraine au cours de sa vie adulte une *inhibition spécifique* (pour employer le terme de M Cohn) (50) de la production des anticorps correspondants apres sollicitation antigenique Que l interpretation de ces faits experimentaux prete a d interessantes discussions dont nous envisageons plus loin ce que nous pensons en etre l essentiel n empeche nullement qu il s agit d un phenomene immunologique primordial

Ainsi la nature immunologique du rejet des homogreffes est aujourd hui definitivement etablie et c est dans le domaine immunologique qu il nous faut envisager les problemes actuellement a l étude

Ces problemes concernent principalement la nature des antigenes en cause la nature des anticorps et le type d hypersensibilite responsables ainsi que le mecanisme intime de rejet du greffon

V NATURE DES ANTIGÈNES EN CAUSE

Le problème de la nature des antigenes d homogreffe » c est a dire des antigenes jouant un role dans l etablissement de l hypersensibilite du receveur vis a vis du greffon est domine par deux elements ces antigenes — ou certains d entre eux — ne semblent présents que *dans certaines cellules*

d information auxquelles sont ramenees les questions concernant les antigenes de greffe

A Cellules vivantes et antigènes de greffe « désensibilisants »

S il est en effet possible d entrainer la sensibilisation a une homogreffe (sous forme d accélération de la mort du greffon) en injectant au futur receveur non seulement des cellules vivantes mais encore des extraits cellulaires purifiés ou un broyat de tissu mort mele a des substances adjuvantes par contre la desensibilisation ne semble pouvoir etre obtenue qu au moyen de cellules vivantes, qu'il s agisse du phenomene de Billingham et Sparrow (31 38) (accroissement du temps de survie d un greffon chez un receveur adulte qui a reçu au prealable des injections intraveineuses de *cellules vivantes du donneur) ou du phénomène de tolérance specifique* acquise (40 41 42) induite par injection intra embryonnaire (ou neo natale) de cellules vivantes du futur donneur

Il existe cependant certains cas ou l on peut augmenter les chances de [illegible] par injection prealable [illegible] ret [illegible] lon [illegible] est constitue de tissu tumoral Ce phénomene a éte baptisé par Snell (51 52) *enhancement phenomenon* terme que l on peut traduire par *phenomene de « facilitation »* Ce phenomene d abord étudie par Casey (53, 54) a fait recemment l objet d importantes etudes de Kaliss (55 a 59) Voici en quoi il consiste si l on greffe par voie sous cutanee une tumeur Sarcome I de souris par exemple (qui se developpe chez des souris de lignée A) sur des souris C 57 la greffe regresse en regle rapidement a partir du 1.e jour Si par contre les souris C 57 sont traitees une semaine avant la greffe de cellules cancereuses par l injection intra peritoneale de tissus morts provenant de souris A les greffons vont proliferer et meme tuer les souris receveuses Les tissus morts entrainant ce phenomene peuvent consister en un homogenat lyophilise de tumeur Sarcome I A ou de tissus normaux de souris A ou en le surnageant d un tel homogenat ou meme en serum de souris A Ce phénomene est un phénomene de nature immunologique specifique du a la formation d anticorps seriques *La « facilitation » de la croissance du greffon* peut etre passivement transmise à des souris C 57 en leur injectant un peu avant de pratiquer la greffe du serum provenant de souris C 57 soumises auparavant a des injections de tissu lyophilise de souris A

Sans entrer dans le detail de l analyse de ce phenomene il est aujourd hui etabli que les anticorps seriques produits par le receveur en reponse à l injection de tissus lyophilisés du donneur agissent sur la tumeur elle même provoquant a son niveau quelque modification qui la rend resistante à la reaction immunologique d hypersensibilite ultérieure du receveur Ceci est démontre par le fait qu une tumeur transplantee chez un receveur ainsi pretraite peut etre retransplantee avec succès chez un nouveau receveur C 57 (donc normalement incompatible) sans qu il soit necessaire de pretraiter ce nouveau receveur Cette modification a donc consiste en une modification de la tumeur Sa I la privant pour ainsi dire de sa specificité de lignée A elle n a pas du tout consiste en une désensibilisation de l hote Un tel phenomene de « facilitation » n a pas pu etre retrouve par Kaliss lui meme pour des greffes de tissus normaux (Il semble cependant que Billingham Brent et Medawar aient obtenu une prolongation du temps de survie

d'homogreffes cutanées par injection préalable au futur receveur de tissu rénal lyophilisé provenant du futur donneur de peau (59 *bis*).

Il n'en reste pas moins que pour modifier le receveur lui-même dans le sens d'une désensibilisation vis-à-vis d'une greffe, les seuls résultats positifs n'ont été obtenus jusqu'ici que par l'*injection de cellules vivantes* du donneur projeté. Ceci s'applique, semble-t-il, aussi bien au phénomène de Billingham et Sparrow (31-38) qu'au phénomène de la tolérance spécifique expérimentalement induite pendant la vie embryonnaire ou néo-natale (40, 41, 42). *C'est ce dernier phénomène, le plus intéressant, dont nous* allons essayer d'analyser maintenant la signification plus particulièrement sous l'angle des connaissances qu'il peut nous apporter en ce qui concerne la nature des antigènes de greffe. La nécessité d'utiliser des cellules vivantes pour l'induire comporte certainement une signification très importante, mais il semble difficile aujourd'hui de préciser cette signification autrement que par l'intermédiaire de l'une des trois hypothèses que nous allons présenter ici et d'après lesquelles les cellules vivantes injectées chez l'embryon joueraient respectivement un rôle « passif », un rôle « semi-actif » ou un rôle « actif ».

PREMIÈRE HYPOTHÈSE. *Les cellules injectées à l'embryon jouent le rôle « passif » de fournisseur d'antigène* et le phénomène de tolérance spécifique acquise au greffon est strictement superposable au phénomène d'inhibition immunologique spécifique (46 à 50), ce dernier constituant évidemment un système beaucoup plus simple mettant en jeu un antigène pur et l'inhibition de la production de l'anticorps correspondant. C'est là l'hypothèse actuellement admise. Il convient alors d'envisager successivement l'interprétation du mécanisme du phénomène d'inhibition immunologique spécifique, puis dans un deuxième temps la raison du caractère particulier « vivant » des antigènes en cause dans le phénomène de tolérance spécifique acquise au greffon, cas particulier du précédent phénomène.

Interprétation du phénomène d'inhibition immunologique spécifique. — L'interprétation de ce phénomène nécessite que l'on ait présentes à l'esprit deux notions importantes.

— La première est que les organismes embryonnaires sont encore incapables de produire des anticorps (60). L'expérience montre de plus que si l'on introduit chez l'embryon un antigène étranger à dose suffisante, quelque chose de durable se produit, dont la conséquence est l'inverse de celle d'une immunisation, tout en demeurant spécifique au sens immunologique du

(*) Notons au passage que ce phénomène apporte une interprétation possible de l'auto-antigénicité habituelle d'éléments comme les spermatozoïdes, la myéline, le cristallin, qui n'ont jamais eu l'occasion de se trouver en présence des cellules mères des futures cellules formatrices d'anticorps pendant la vie embryonnaire. La persistance de cet isolement pendant la vie adulte expliquerait encore que cette auto-antigénicité n'ait pas dans les conditions normales l'occasion de donner lieu à une réponse immunologique.

spécifique et l induction spécifique (50) ce dernier terme désignant l action inductrice d un antigène sur toute cellule formatrice d anticorps Les deux hypothèses maîtresses concernant la formation et l élaboration continue des anticorps sont les suivantes la première ou théorie du « moule » de Breinl et Haurowitz (61) Mudd (62) Alexander (63) et Pauling (64) d après laquelle l anticorps se moulerait pendant sa formation sur l antigène présent dans la cellule implique que l antigène demeure à la disposition de la cellule formatrice d anticorps la deuxième ou théorie de la modification enzymatique de Burnet et Fenner (65) d après laquelle les anticorps seraient élaborés et modelés par un système enzymatique susceptible de subir une modification adaptative vis à vis de l antigène (comparable aux modifications adaptatives des enzymes bactériens) Cette modification adaptative une fois réalisée serait persistante et la synthèse d un anticorps pourrait se poursuivre en l absence de l antigène correspondant

Avec ces deux notions considérons maintenant le phénomène d inhibition (ou de tolérance) spécifique Les deux mêmes mécanismes semblent également pouvoir jouer sans que l on puisse véritablement choisir avec assurance entre les deux ou bien c est la théorie des enzymes adaptatifs qui s applique et dans ce cas l introduction d un antigène étranger che l embryon déterminerait au niveau des cellules mères des futures cellules formatrices d anticorps une modification enzymatique définitive modification excluant la possibilité de donner ultérieurement aux molécules anticorps une certaine configuration (celle qui précisément correspond à l antigène en question) et dans ce cas l antigène n a pas besoin de persister pour que l inhibition acquise demeure en permanence Ou bien c est une théorie comparable à celle du « moule » et alors l inhibition spécifique de la production d un anticorps ne peut être réalisée que par une pression permanente de l antigène correspondant ce qui implique sa présence permanente

Dans ce dernier cas il n y aurait peut être pas de *différence essentielle* entre le phénomène d inhibition (ou de tolérance) spécifique acquise (pendant la vie embryonnaire) et le phénomène de *paralysie immunologique* décrit par Felton (66) qui injectant à la souris adulte des doses importantes de polysaccharide pneumococcique constate que l animal ne peut plus fabriquer d anti corps contre le polysaccharide injecté mais qu il peut en fabriquer normalement contre un autre antigène Cette incapacité spécifique s accompagne de la présence du polysaccharide en question dans les tissus de l'animal (67) Certes sous l influence des travaux de Dixon (68) « on admet habituellement que le phénomène de Felton met en jeu la neutralisation continue de l'anti corps alors que l inhibition (ou tolérance) spécifique met en jeu l inhibition directe de la synthèse de l anticorps mais il n existe pas de preuve absolue que la « paralysie immunologique » ne met pas en jeu une inhibition de synthèse ou que l inhibition (ou tolérance) ne met pas en jeu une neutralisation de l anticorps Les deux phénomènes pourraient donc bien être les manifestations d un même mécanisme fondamental » (M Cohn) (50)

Dans ces conditions la nécessité d injecter des cellules vivantes pour entraîner une tolérance ultérieure vis à vis d une greffe provenant du même donneur de cellules pourrait s expliquer de l une des manières suivantes sur ... *indéfinie* des antigènes est ou n est

nécessaire à l établissemen

d un etat de tolerance on conçoit l utilité d injection de cellules vivantes Cette persistance serait alors facilement assurée par la survie des cellules injectées chez l embryon La necessité de la presence des cellules vivantes se concevrait d autant plus que les antigenes en cause sont peut etre peu resis tants et assez rapidement detruits On peut apporter à l appui de cette hypo thèse les résultats des experiences de Green et Lorincz (69) montrant que l exposition précoce et massive d embryons de poulets aux antigènes d une tumeur en voie de croissance n est pas en soi une condition suffisante a la production d un état de tolerance definitive vis a vis de ces antigenes puis-que les cellules tumorales après avoir prolifere pendant la vie embryonnaire du receveur, régressent au moment de l eclosion et qu a l age de deux mois les poulets sont capables de repondre à l injection du meme type de cellules tumorales par une fabrication d anticorps aussi importante que celle des temoins Ces auteurs pensent donc que « la condition de tolérance provoquee par des cellules homologues dépend de leur survie permanente chez le rece veur »

b) Si la persistance indéfinie des antigenes n est pas necessaire a l établis sement d un etat de tolérance on peut interpréter la necessite de l injection de cellules vivantes par l intervention de facteurs qualitatifs ou quantita tifs Ces facteurs concernent respectivement le nombre et la qualité des antigenes presents dans le matériel injecté et la quantité d un antigene donné necessaire à entrainer la tolérance

1 *Nombre et qualité des antigènes présents* le fait de tuer les cellules detrui rait par une autolyse rapide certains antigenes existant dans les tissus vivants L organisme (embryonnaire) n aurait donc pas l occasion de devenir tolérant vis a vis de ces antigenes Lorsque plus tard l organisme etant sorti de la periode neo natale sera devenu immunologiquement mature et qu on pratiquera sur lui une greffe de tissu vivant provenant du meme don neur (ou de la meme lignee « homo ygote ») les antigenes en question pre sents dans ce tissu vivant seront capables d immuniser ce receveur ce qui entrainera le rejet de l homogreffe Ceci est l expression d une loi inhérente meme au concept de la tolérance specifique acquise (interpretee comme une variante complexe de l inhibition immunologique specifique) et qui est la suivante alors qu un seul antigène commun au futur greffon et au materiel injecté au futur receveur (cellules vivantes cellules mortes ou extrait cellu laire) entrainant la formation de « l anticorps » (anticorps serique ou pro priété liée aux cellules) correspondant peut suffire a entrainer l hypersensi bilite vis a vis du greffon et l accélération de son rejet par contre l eta blissement d un etat de tolerance acquise vis a vis d un greffon nécessite l utilisation de tous les antigenes susceptibles de jouer ulterieurement un role dans l hypersensibilité de greffe Cette première possibilité n est pas invraisemblable car la difference entre une cellule vivante et une cellule morte réside avant tout dans une désorganisation des rapports biochimiques desorganisation qui va forcement de pair avec des modifications irreversibles de certains des constituants essentiels de la cellule Cette hypothese tendrait à indiquer que les antigènes d homogreffe (ou du moins certains d entre eux indispensables au meme titre que les autres à l établissement d une tolérance acquise) sont particulièrement fragiles et labiles Une fois ce role d apport d antigènes labiles propres aux cellules vivantes rempli les cellules injec

tées pourraient mourir sans empecher le processus de tolérance de se perpétuer une fois induit

2 *Quantité d'antigene nécessaire à entrainer la tolérance* un raisonnement de meme ordre se rapportant non plus au nombre des antigènes mais au nombre des cellules du receveur mises en contact avec l antigene montre clairement que toutes les cellules meres des futures cellules formatrices d anticorps doivent etre mises en presence des antigenes vis a vis desquels on veut obtenir une tolerance immunologique, alors que chez le sujet immunologiquement mature il suffit qu une proportion relativement faible des cellules « immunologiquement competentes » soit mise en contact avec le ou les antigenes pour que se trouve declenché le mécanisme de formation des anticorps correspondants Il est donc logique de penser que la quantite d un antigène donné necessaire à entrainer la tolerance specifique acquise doit etre superieure à celle qui est suffisante à entrainer l immunisation Or la quantité ponderale (et non plus seulement le nombre cette fois-ci) des antigenes produits par des cellules vivantes et capables de se reproduire meme pendant une période limitee est beaucoup plus grande que la quantité fournie une fois pour toutes par le meme nombre de cellules mortes ou un extrait cellulaire correspondant C est precisement ce phenomene qui a longtemps fait penser jusqu aux travaux de Saenz (70) et de Coulaud (71) que l hypersensibilité au bacille tuberculeux ne pouvait etre induite que par des bacilles vivants L intervention de ce deuxieme facteur quantitatif n est pas illogique S il est effectivement en cause et seul en cause des quantites plus grandes de cellules mortes doivent etre capables d entrainer le meme résultat que des cellules vivantes injectees en quantité moderée Mais ce facteur (qui suppose la persistance des cellules injectees au moins un certain temps) n exclut pas du tout la possibilite d intervention des autres facteurs

L intervention éventuelle des differents facteurs que nous venons d envisager est soumise à l acceptation de l hypothèse suivant laquelle les cellules injectees jouent un role « passif » d antigene Mais il est possible d envisager d autres hypothèses ou la signification du phenomène de tolerance spécifique acquise à l homogreffe est radicalement differente de celle du phénomène d inhibition specifique concernant les antigenes purs

DEUXIÈME HYPOTHÈSE *Les cellules injectées a l embryon jouent un rôle « semi actif » de fournisseurs ou de modificateurs d organites intracellulaires du receveur*

Selon cette hypothese les cellules du receveur meres des futures cellules formatrices d anticorps verraient leurs mecanismes de synthèse proteique modifies ou partiellement remplaces par les mecanismes correspondants des cellules injectees Ce mecanisme diffère de celui invoqué par la théorie de la modification adaptative enzymatique par le fait qu il met en jeu non pas une *réaction* des mecanismes cellulaires du receveur mais une *induction* ou un *remplacement* aboutissant a une modification profonde d au moins une partie de ces mécanismes

On peut invoquer en faveur de la possibilite d un tel mécanisme les experiences d Avery (72) transformant des pneumocoques de type A en pneumocoques de type B par simple addition a la culture de type A d acide désoxyribonucleique extrait du type B, ou encore les expériences plus recen

tes et portant sur des organismes infiniment plus complexes (canards) de Benoit et coll (73) et aboutissant a des modifications importantes dans les mécanismes de synthese avec modifications morphologiques correspondantes

Si une telle hypothése était exacte on devrait pouvoir remplacer les cellules vivantes par un extrait cellulaire et c est naturellement aux désoxyribonucléoprotéines (intactes de preference à l acide désoxyribonucléique) que l on pense Cependant jusqu ici les tentatives pratiquees avec des noyaux ou des extraits nucléaires actifs pour conferer l hypersensibilite au greffon (Billingham Medawar) (74) et de l acide désoxyribonucléique (Hašek) (75) se sont *soldées par des echecs*

Quant à l hypothese suivante elle est beaucoup plus proche de celle ci que de la premiere elle fait jouer un role actif et permanent aux cellules injectées a l embryon

Troisième hypothèse *Les cellules injectees à l embryon jouent un rôle actif et permanent de remplacement*

Cette derniere hypothe e demande a etre presentee avec autant de prudence que la précédente et ne s applique peut être pas a tous les cas de tolerance acquise En effet si les cellules vivantes injectées a l embryon ne sont pas des cellules « immunologiquement competentes » (ni susceptibles de le devenir dans leur *nouvel environnement*) alors leur persistance meme indefinie ne saurait avoir d autre signification que celle envisagée dans la première hypothese (ou beaucoup plus improbablement dans la deuxième) Mais il n est pas certain que ce cas ait jamais eté observe Si par contre les cellules vivantes injectées chez l embryon sont immunologiquement competentes il en va tout autrement et un nouvel enchainement d événements prend place propre à donner a l interpretation du phenomene de tolérance spécifique acquise une signification tres particulière et n avant absolument rien a voir avec le phénomene d inhibition specifique concernant les antigenes purs Ces cellules en effet vont se reproduire se disseminer dans les organes lymphoides coloniser les centres immunologiques adultes et immunologiquement actives ces cellules placées en presence d antigenes nouveaux vont repondre non pas par une tolerance acquise comme les cellules embryonnaires sont censées le faire mais par une elaboration d anticorps (ou du moins une reaction immunologique specifiquement dirigee contre l antigene provocateur) Les antigenes les plus immediats sont contenus dans le tissu lymphoide embryonnaire que colonisent les cellules adultes Un tel conflit ne va pas aller *sans conséquences pathologiques ces conséquences se font* sentir principalement sur le systeme lymphoide et hematopoiétique comme l a démontré Simonsen (76 77) parfois elles vont meme jusqu a compromettre le developpement et la vie de l animal apres sa naissance comme l a décrit Billingham (18 78) chez la souris donnant a l en emble du tableau le nom de « maladie des avortons » (runt disease) Mais il faut reconnaitre que *dans nombre de cas cet effet adverse est peu marqué en dehors d un certain* degré d involution ganglionnaire Ces animaux sont des « chimeres » conformément à la terminologie des immuno hématologistes Naturellement ils

n'est pas assimilable au rôle purement passif d'un antigène persistant dans les tissus du receveur mais que ce rôle est actif dans la reconnaissance des antigènes de greffe (de même origine qu'elles) et, éventuellement dans la transmission du message concernant cette reconnaissance aux autres cellules des centres immunologiques

Une situation de signification analogue peut être créée expérimentalement chez des animaux adultes irradiés par une dose léthale de rayons X qui détruit leur système réticulo endothélial lymphoïde et hématopoïétique puis protégés par une injection de cellules de moelle osseuse provenant d'autres animaux non irradiés (79 80 81) Ces cellules remplacent en particulier dans leur rôle hématopoïétique, les cellules du receveur neutralisées par l'irradiation Les animaux ainsi traités sont dans une forte proportion protégés contre l'action léthale de l'irradiation La suite des événements est alors différente suivant l'origine des cellules de moelle osseuse injectées si ces cellules provenaient d'animaux de la même lignée très pure que le receveur ce dernier a de fortes chances de survivre indéfiniment Si les cellules provenaient d'animaux d'une autre lignée (ou parfois même d'animaux d'une autre espèce) (82) alors temporairement au moins les receveurs de cellules deviennent capables d'accepter une greffe de tissu des animaux donneurs de cellules (83) Puis certains d'entre eux vont mourir vers la troisième semaine Des arguments existent montrant que cela est dû à une réaction du receveur ayant récupéré sa capacité de former des anticorps contre les cellules étrangères injectées (Trentin 84) D'autres vont au cours d'une période allant du 35^e au 50^e jour suivant l'irradiation présenter une maladie
[illegible] si les cellules
due à une
[illegible] ette mala
[illegible] guérissent
et peuvent persister à l'état de « chimères » avec une population lymphoïde et sanguine mixte (85) Cette situation reproduit donc chez l'adulte ce que nous venons de voir chez l'embryon et l'on a ici la certitude qu'il ne s'agit pas d'une tolérance induite chez le receveur mais du remplacement des mécanismes immunologiques par ceux du donneur (*)

Ainsi cette dernière hypothèse diffère profondément de celle qui attribue à la tolérance spécifique acquise au greffon la même signification qu'à l'inhibition immunologique spécifique d'un antigène pur *Elle en diffère* essentiellement parce que les cellules injectées pendant la vie embryonnaire ne modifieraient pas le mécanisme immunologique du receveur par l'intermédiaire d'un antigène agissant à la phase « d'adaptabilité immunologique » mais qu'elles se substitueraient partiellement au moins à ces mécanismes

(*) Remarquons au passage que le traitement d'une leucémie se basant *sur* les expériences précédentes devrait strictement répondre aux deux exigences suivantes 1° irradiation à dose léthale pour éliminer totalement non *seulement les cellules* leucémiques mais encore les cellules immunologiquement compétentes du sujet 2° remplacement du tissu lymphoïde et hématopoïétique détruit par du tissu *homologue* correspondant mais d'origine embryonnaire (rate embryonnaire serait le mieux) [illegible] homologue si souvent mortelle et *ceci grâce à la* [illegible] rantes aux antigènes *qu'elles* [illegible] ible donc très difficile d'ens

Cette hypothèse ne peut naturellement s appliquer qu au cas ou les cellules injectées chez l embryon sont des cellules immunologiquement competentes ou susceptibles de donner naissance à des cellules elles memes immunologiquement competentes Si les cellules injectees sont dans l incapacite definitive de produire des anticorps et entrainent pourtant l etablissement d une tolerance spécifique acquise au greffon du meme donneur on doit alors accepter l assimilation de ce phénomene *a celui d inhibition specifique* comme constituant la seule explication possible

Mais il semble bien que jusqu à present du moins la tolérance specifique acquise n ait pu etre induite que par des injections intra embryonnaires comportant des cellules vivantes capables de se reproduire et immunologiquement compétentes ou apparemment susceptibles de le devenir (au moins dans leur descendance) sang total par voie intraveineuse (parabiose embryonnaire Hasek 43 44 86) sang total par voie non intraveineuse donnant une tolérance plus faible (Billingham Brent et Medawar 87) sang total par voie intraveineuse chez le nouveau né (Woodruff 88) suspensions de cellules spléniques chez l embryon (Billingham Brent et Medawar 40 41) ou chez le nouveau né (Woodruff et Simpson 42) fragments de tissu renal ou testiculaire (Billingham Brent et Medawar 40 41) Il semble bien par contre que les cellules ne possédant aucune capacite d elaborer des anticorps aient abouti jusqu ici à des échecs hematies (Medawar 74) et meme hématies nucléées (Hasek) Les spermatozoides ont semble donner une tolerance faible (Hasek 75) mais Hasek lui meme pense qu elle pourrait bien être due aux cellules contaminant les spermatozoides Quant aux cellules tumorales elles semblent donner des resultats allant dans le meme sens puisque Koprowski (89) a pu obtenir une tolérance acquise vis à vis de cellules lymphosarcomateuses alors que Green et Lorincz (69) n obtenaient pas de tolérance vis a vis de cellules epitheliomateuses

Dans ces conditions il *semble intéressant a titre péculatif disons meme* « provocatif » d evoquer la possibilité suivante compatible avec tous les faits présentés le mecanisme commun que l on prete habituellement aux deux phénomenes de tolérance specifique acquise a l homogreffe et d inhibition immunologique spécifique d un antigène pur *mécanisme con i tant a* se faire « reconnaitre et accepter » par l appareil immunologique du receveur e à devenir consideré par lui comme faisant partie integrale du meme individu n existerait pas En d autres termes il n existerait pas reellement de phase « d adaptabilite immunologique » le phenomène *d inhibition spécifique* nécessiterait la présence continue de l antigène et serait superposable au phénomène de Felton (dit de paralysie immunologique) et le phénomène de tolérance acquise serait du au remplacement *au moins partiel* du systeme immunologique du receveur par les cellules injectées

Il serait cependant prematuré de choisir a l heure actuelle entre les trois hypotheses présentées ci dessus d autant plus que l hypothese assimilant tolérance acquise et inhibition spécifique reunies en un meme concept aboutit à des conclusions logiques et cohérentes en accord avec celles auxquelles aboutira le chapitre suivant concernant les caracteres particuliers de certains des antigenes d homogreffes ce seraient des antigènes particulièrement fragiles et labiles très vraisemblablement liés aux mécanismes de synthèse cytoplasmiques et plus particulierement à des substances tenant de très pres aux nucléoproteines Rappelons d ailleurs que des noyaux isolés

sont capables sinon d'entraîner la tolérance spécifique après injection à l'embryon du moins d'entraîner chez l'adulte l'hypersensibilité vis à vis d'une greffe ultérieure en provenance du même donneur (74) Il en va de même pour certaines substances nucléoprotéiques extraites de ces noyaux (74)

En définitive ce sont les mêmes mécanismes liés à la synthèse cytoplasmique qui semblent être en cause dans le phénomène de la tolérance spécifique acquise à l'homogreffon, quelle que soit l'hypothèse adoptée concernant leur rôle chez le receveur rôle purement passif d'antigène rôle « semi actif » d'induction active ou rôle purement actif de substitution

B Antigènes d'homogreffe et spécificité d'individu

[illegible] la

Une remarque importante s'impose valable tout au long de cet exposé lorsqu'on pratique des homogreffes sur des animaux appartenant à une même lignée de très haute pureté génétique les individus de par l'identité de leur patrimoine génétique sont tellement semblables les uns aux autres qu'ils ne sont pas susceptibles de réagir immunologiquement l'un contre l'autre ainsi les isogreffes survivent à peu près comme des autogreffes et sont souvent pratiquées au lieu d'autogreffes dans les études immunologiques auxquelles nous nous référons Évidemment les homogreffes pratiquées entre animaux de lignées différentes sont rejetées En quelque sorte la spécificité d'individu est ici remplacée par une spécificité de lignée pure les animaux appartenant à une même lignée très pure étant pour ainsi dire interchangeables Ceci modifie peu la signification générale du problème

Quelles sont, en effet les implications des faits précédents en ce qui [illegible] antigenes [illegible] me [illegible] en [illegible] concernant les auto antigenes Les raisons d'une telle confrontation (90) résident dans les points communs qui unissent les auto antigenes et les antigenes de greffe Ces points communs sont principalement les suivants dans les deux cas il s'agit d'antigenes cellulaires ou tissulaires induisant l'apparition de propriétés spécifiques ayant les caractères d'anticorps (extra cellulaires ou dits « sessiles ») cytotoxiques De plus les trois endroits où l'on peut pratiquer des homogreffes viables (chambre antérieure de l'œil (9 91), substance blanche à l'écart des ventricules et des méninges (9 9 93 94) et testicules (95 96 97) ou vesicules séminales (98)) sont précisément les trois endroits où il est avéré que l'on peut trouver des auto antigenes [cristallin (99) substance blanche cérébro médullaire (100 101) et spermatozoïdes (102 à 106)] Enfin comme nous l'avons déjà mentionné le phénomène de tolérance spécifique acquise naturelle ou artificielle dont nous avons vu le rôle dans la survie des homogreffes semble en rapport direct avec l'absence ou l'existence de pouvoir auto antigénique dans une substance ou une cellule La comparaison entre auto antigenes et antigenes de greffes [illegible] espoir de recueillir des éléments [illegible] blèmes

Cette spécificité

d organe est independante de toute specificite d individu et meme jusqu a un certain point de la spécificite d espece En effet (90 107) un auto antigene entraine la formation d un anticorps capable d agir sur un antigene autologue (provenant du sujet meme qui a elabore l anticorps) c est a dire comme auto anticorps mais ce anticorps est egalement capable d agir sur un antigene homologue (provenant d un autre sujet de meme espece) c est a dire comme iso anticorps il peut parfois meme agir sur un antigene heterologue (provenant d un sujet d espece differente) c est a dire comme hetero anticorps Reciproquement la production d un auto anticorps (c est a dire d un anticorps capable de reagir sur une substance appartenant a l organisme meme qui a élabore cet anticorps) peut etre entrainee par injection d un auto d un iso ou meme d un hetéro antigene Dans tous ces cas le seul point commun a ces differents antigenes est la similitude de l organe employe il y a donc specificite d organe stricte dans le systeme auto antigène auto anticorps Cette specificite d organe est vraisemblable ment liée a des substances jouant un role dans la fonction particuliere a l organe (ou au tissu ou au systeme ou au groupe de cellules) considere Il est egalement probable qu elle n est pas due a des proteines (ou du moins aux proteines normales communes) il est en effet difficilement pensable que le mecanisme de synthese des proteines (dont la specificité est determinee génetiquement) puisse élaborer des substances proteiques qui seraient capables d exciter en retour ce meme systeme a former des proteines anticorps specifiquement dirigees contre les substances proteiques initiales Si par contre ces substances proteiques sont denaturees » d une maniere ou d une autre ou modifiees par exemple par l adjonction d un groupement prosthetique ayant une signification fonctionnelle (comme c est le cas pour la thyroglobuline) on conçoit mieux la possibilite d une auto antigenicite la thyroglobuline se revele effectivement auto antigenique On conçoit encore mieux qu une substance non proteique soit auto antigénique En ce qui concerne l auto antigene présent dans les spermatozoides nous avons apporte avec F Toullet et P Maurer (90) des arguments experimentaux eliminant une nature protéique et suggérant une nature polysaccharidique ou glycoproteique (a courtes chaines polypeptidiques)

Les antigenes de greffe par contre s ils ne sont pas partages par tous les individus d une espece et encore moins par des individus d espece differente puisqu ils sont specifiques d individu sont a l inverse partages par des types tres differents de cellules appartenant a un individu (13 53) Ils existent semble t il dans toutes les cellules vivantes capables de synthese protoplasmique qui ont éte testees jusqu ici Bien qu il soit difficile d obtenir un type cellulaire pur ceci a ete realise au moins pour les cellules epitheliales malpighiennes (31 58) et les cellules leucocytaires (13) qui partagent ces memes antigenes également presents dans la peau (3 33) le rein (33 34 108) et la rate (34) (et tres certainement de nombreux autres organes tissus ou cellules) Ces memes antigenes semblent par contre absents des cellules qui sont incapables de synthetiser du protoplasme c est le cas pour les hematies (74) et nous a t il semble pour les spermatozoides (90) C est ici que revient a l esprit la nécessite d employer des cellules vivantes pour entrainer le phenomene de tolérance spécifique Cet ensemble de faits suggere fortement que les antigenes d homogreffes a l oppose des auto antigènes sont intimement liés aux mécanismes cellulaires de synthese protoplasmique

c est à dire, avant tout, protéique Il suggère aussi que ce sont precisément les memes facteurs qui permettent a certaines substances protoplasmiques de jouer le role d *antigene de greffe et qui font que ces substances ne peuvent* pas etre auto antigeniques Cette spécificité d individu dependant du patri moine génetique de chaque individu (ou de chaque souche animale tres pure) dirige naturellement les recherches vers l appareil chromosomique De fait des etudes portant principalement sur les tumeurs transplantables des souris ont montre que la possibilité de prise de ces greffes d un individu a un autre etait essentiellement sous la dependance de genes qui ont ete nommés genes d histocompatibilité » Les mieux étudiés ont e e localises ave une grande pré ision au niveau du lo us H2 Ces etudes (109 à 115) qui apporte ront certainement d importants elements dans la connaissance des phéno menes determinant la spécificite d individu ne donnent cependant pas la clef immunologique de la nature des antigènes d homogreffes car s il est devenu assez courant de parler d antigenes du locus H2 il s agit là d une formule elliptique car l existence de tels antigenes dans la cellule peut tre bien etre determinee par la présence de ces gènes sans que ces derniers e soient le support materiel C est pourquoi si les belles recherches d Medawar lui font actuellement penser que les antigenes de greffe sont pro bablement de nature desoxyribonucleoprotéinique (74) il est peut etre plu prudent de s en tenir actuellement a la notion d antigenes *lies aux mecanisme de synthese protéique* Une des autres raisons qui nous poussent à de telle conclusions est que nous avons ete incapables de déceler la présence d anti genes d homogreffe dans les spermatozoides d un animal *alors* que nous pouvions les déceler dans ses leucocytes (90) (en utilisant comme tes le phenomene du « second set » d acceleration de la mort du greffon) Or les spermatozoides presentent divisé en deux dans chaque spermatozoide mais complet dans un echantillon de sperme l ensemble du materiel chromoso mique présent dans les noyaux des cellules somatiques du sujet Par contre ils ne possedent pas la possibilite de synthétiser du protoplasme Il ne nous semble pas invraisemblable que la specificite d individu prenne nais ance avec l individu lui meme c est a dire au moment où le spermatozoide ayant fecondé l ovule le stock diploidique normal du noyau se trouve reconstitue et ou le mecanisme de synthèse protéique soudain s eveille Il n est en effet pas impossible que les antigenes specifiques d individu ne soient pas directement supportés par des genes chromosomiques mais qu ils soient la conséquence (peut etre intracytoplasmique) de l interaction de genes com plémentaires d origine paternelle et maternelle La possibilite que de nou veaux antigenes puissent naitre de l interaction de deux gènes a reçu récem ment d importants arguments expérimentaux (116) Cependant de telles considerations ne peuvent avoir actuellement que le sens d une hypothèse de travail

C Autres facteurs possibles

Si les faits precedents resument ce que l on connait actuellement sur les antigenes de greffe il n est pourtant pas impossible que d autres antigenes puissent eventuellement jouer un role Nous en donnerons ici trois exem ples

1° Nous avons vu qu un sérum de lapin anti peau de cobaye pouvant

accelerer la mort d une homogreffe de peau d un cobaye quelconque à un autre cobaye (28) L intervention d un systeme antigene anticorps specifique d espece peut donc jouer un role dans le rejet d une homogreffe mais il s agit ici d une situation hautement artificielle

2° Chez des animaux presentant une dermatose que l on a pu attribuer a une auto sensibilisation anti peau une autogreffe peut subir une mortification partielle (28) ce qui suggere la possibilité de l intervention d anticorps anti-organe (anti peau dans le cas present) dans le rejet d une greffe Ici encore il s agit d une situation artificielle

3° Il n est pas impossible enfin que des antigenes specifiques de sexe lies au chromosome Y puissent jouer un role dans le rejet de certaines homogreffes Eichwald et coll (23) en effet ont constate chez des souris de lignée tres pure (A/Jax et C 57 BL) ou l isogreffe est couronnee de succes dans le sens mâle a mâle femelle a femelle ou femelle a mâle que l isogreffe de peau d un mâle a une femelle est en genéral vouee a l echec et qu une deuxieme isogreffe de mâle a femelle est rejetee plus vite qu une premiere (phenomene de second set) Nous meme avec F Toullet et P Maurer (90) avons constate que dans certains cas une injection intradermique de spermatozoides de lapin à une lapine entrainait chez cette dernière une acceleration du rejet d une homogreffe de peau male mais ce phenomene ne s est pas revele constant et demande une analyse plus poussee (role de facteurs endocriniens par exemple)

Mais en définitive les antigenes d homogreffe qui jouent le role determinant dans les conditions habituelles sont veritablement *specifiques d individu* — ou bien specifiques de lignees pures tendant a l homozygotie ce qui revient a peu pres au meme les differents individus de la lignee tendant a etre « interchangeables » en dehors des caracteres lies au chromosome sexuel Cette specificite d individu des antigenes d homogreffes rapprochee du caractere nécessairement vivant des cellules utilisees en vue de la désensibilisation specifique suggere que les antigenes d homogreffe sont intimement lies aux mecanismes de synthese des proteines ces deux points capitaux — specificite d individu et liaison aux mecanismes de synthese des protéines — les opposent strictement aux auto antigenes (90)

VI NATURE DES ANTICORPS ET TYPES D HYPERSENSIBILITÉ RESPONSABLES

Peut etre conviendrait il de dire plutot d une maniere plus generale nature de la reaction immunologique responsable du rejet du greffon Nous envisagerons d abord *les rapports entre ces phenomènes immunologiques* et les deux types classiques d hypersensibilite pour essayer ensuite de nous livrer a une analyse objective de l hypersensibilité « de type homogreffe

A Rapports avec les types immédiat et retardé d hypersensibilité

La question a éte tres débattue ces dernières années de savoir si la réaction immunologique qui aboutit au rejet du greffon est due à l établissement chez

le receveur d un etat d hypersensibilite allergique de type immediat ou de type retarde

Dans l hypothese d une hypersensibilite de type immediat ou anaphylactique ayant pour médiateurs des anticorps seriques en partie liés aux cellules sensibles et ou les phénomènes allergiques débutent au niveau des parois vasculaires et des muscles lisses le rejet du greffon prendrait une signification semblable a celle du phénomene d Arthus

Dans l hypothese d une hypersensibilite de type retarde ou bactérien ayant pour médiateurs quelques mysterieux anticorps « sessiles » (proprietes ayant la meme specificite immunologique que les anticorps mais semblant liées aux cellules — lymphocytes et histiocyto macrophages) et ou les phenomenes allergiques semblent debuter directement au niveau des cellules sensibilisees sans intermédiaire vasculaire le rejet du greffon se ferait suivant un mecanisme rappelant celui du phenomene de Koch

On a rapidement trop rapidement peut etre nie tout rapport avec l hypersensibilite de type anaphylactique car elle est insuffisante à expliquer le rejet des homogreffes et d autre part les elements n en sont habituellement *pas retrouves chez le receveur*

Par contre beaucoup d auteurs ont considere que le phenomene du rejet de l homogreffe était probablement une manifestation d hypersensibilité allergique de type re arde Les arguments en ont été excellemment réunis recemment par H Sherwood Lawrence (117)

I ARGUMENTS EN FAVEUR DE L ASSIMILATION DU REJET DE L HOMOGREFFON A UNE RÉACTION D HYPERSENSIBILITÉ DE TYPE BACTÉRIEN

Ces arguments sont les suivants

— Necessité dans les deux cas pour induire l *hypersensibilite d employer* un materiel vivant intact (greffe ou bacille) ou un materiel mort mais en grande quantité ou avec l aide d adjuvants (Saenz 70 Coulaud 71 Freund [illegible] Voisin et Maurer, 27 [illegible] inalement possibilite [illegible] 120 N Choucroun 121 Raffel 122 Freund 123 Gell et Hinde, 124 Tremaine et Jeter 125 Metaxas 126 pour les antigenes bacillaires ou proteiques et Billingham et Sparrow 328 Medawar 74 pour les antigènes de greffes) avec beaucoup plus de chances de succès en utilisant la voie intradermique plutot que la voie intra veineuse

— Delai d apparition du phenomene et sa ressemblance avec le phénomene de Koch

— Absence d anticorps seriques responsables mesurables (Mitchison 12, Medawar, Voisin et Maurer 27 28 Gaudino 129 et beaucoup d autres)

— Echec habituel du transfert passif de l hypersensibilite responsable par le serum (Medawar Mitchison et d autres) à l exception peut etre de la leucemie (Amos et Day 130)

— Succes du transfert passif ou plutot du transfert « adoptif » pour utiliser [illegible] au moyen des cellules ganglionnaires [illegible] 131 Billingham Brent et Meda [illegible]

— Corrélativement le role primordial des cellules est confirmé par les expériences du type chambre poreuse (Algire et coll 10 132 133 134

Woodruff) ou par des expériences montrant que des cellules provenant d animaux transplantes sont capables de modifier ou d absorber des anti gènes de greffe en provenance du donneur du transplant (Berrian 136)

Tous ces elements communs a l hypersensibilite de type bacterien et à l hypersensibilité en cause dans l échec des homogreffes ont conduit plusieurs auteurs a penser que cette derniere n etait qu une manifestation particuliere de la premiere *Il existe cependant des divergences qui n autorisent pas cette assimilation*

2 ARGUMENTS CONTRE L ASSIMILATION DU REJET DE L HOMOGREFFE A UNE RÉACTION D HYPERSENSIBILITÉ DE TYPE BACTÉRIEN

L essentiel des arguments precedents se ramene au role primordial des cellules (lymphocytes plasmocytes ou macrophages) dans le rejet du greffon compare avec l absence apparente de role du serum

Or meme si ces affirmations étaient strictement exactes elles ne signifie raient pas nécessairement qu il s agit d un phenomène d hypersensibilite retardee

Par ailleurs elles se revelent partiellement inexactes l absence d anticorps seriques chez les sujets homogreffes qui a longtemps ete un dogme se revele *sujette a des exceptions de plus en plus frequentes Certes les anticorps* complets classiques tels que les anticorps precipitants sont absents encore que certains resultats encore non confirmes aient pu sembler en montrer l existence en faible quantite (Bollag 32) Par contre les anticorps incomplets hemagglutinants sont de plus en plus frequemment retrouves en general dans les homogreffes tumorales (Hauschka 135 Gorer 29 138 Mitchison et Dube 139 et d autres) mais parfois aussi dans les homogreffes de tissus normaux (Simonsen 34 Gorer 30 Amos et coll 140) Des anticorps agglutinant les leucocytes sont parfois retrouves dans les homogreffes de tissus cancéreux et normaux (Amos 141 Gorer 30) Bien plus des anticorps cytotoxiques ont ete trouves dans les homogreffes leucemiques chez la souris (Amos et Day 130) et des anticorps « cytostatiques » (absence de developpe ment « in vivo » de cellules precedemment traitees « in vitro » apres incubation avec de tels serums) *ont été mis en evidence dans des homogreffes de tissus* tumoraux (Gorer 142 Mitchison et Dube 139) et normaux (Billingham 31 Woodruff 135) Nous envisagerons plus loin les implications des expe riences conduites *specialement pour etudier le role des anticorps dans le rejet* des homogreffes de tissus normaux (Voisin et Maurer 27 28 Stetson et Demopoulos 119) ainsi que les rapports possibles entre l existence d anti corps *seriques et le rejet d une homogreffe*

De plus le role primordial joue par les cellules dans le rejet des homogreffes n est peut etre pas exactement de meme nature que le role egalement pri mordial *qu elles jouent dans* l hypersensibilite de type retarde Un important argument en faveur de cette opinion est le suivant il est généralement admis que des cellules sensibilisées prelevees chez des animaux ayant une hypersensibilite de type bacterien sont endommagees lorsqu on les met en presence « in vitro » de l antigene correspondant (capable de donner lieu à une intradermo reaction retardee) comme l a montre Rich (143) confirmé par d autres auteurs (144 à 147) malgré quelques experiences contradictoires (148 149) Or un tel phenomene n a pas eté retrouve dans l hypersensibilite

en cause dans l echec des homogreffes (117) (Medawar 148 Voisin Toullet et Maurer 150)

Une dernière et tres importante objection est apportee par les cas d agammaglobulinemie de signification quasi experimentale L'agammaglobulinemie extensivement etudiee par R Good ces dernières annees est une maladie qui dans sa forme essentielle est congenitale et semble transmise par un gène recessif uniquement chez les sujets mâles Elle est caracterisee par l ab ence de synthese globulinique et l incapacite de repondre à une sollicitation antigenique par une proliferation plasmocytaire avec formation de globulines anticorps Par contre ces sujets sont capables d acquerir une hypersensibilité de type bacterien ou retardé comme cela a ete demontre vis a vis de la tuberculine (Zinneman et coll 151 Seltzer et coll 152 Porter 153 154) du 2 4 dinitrofluorobenzene (Porter 154 Good et coll 155) et une reponse accelerée typique suivant une seconde vaccination (Porter 155)

Or fait capital ces sujets agammaglobulinemiques incapables d acquérir une hypersensibilite de type immediat et capables d acquerir une hypersensibilite de type re arde sont incapables de rejeter un homogreffon si bien que les homogreffes prennen chez eux, a peu pres comme des autogreffes (Good et coll , 26)

Si ces faits ne peuvent pas faire considerer que le rejet d une homogreffe est due à une hypersensibilite de type immédiat pas plus d ailleurs qu a une simple action cytotoxique directe d anticorps ériques par contre ils montrent a l evidence que ce rejet ne peut pas etre ramene a une manifestation d hypersensibilité de type bacterien ou bien il s agit de deux phénomenes differents ou bien le rejet d une homogreffe necessite l intervention d un ou de plusieurs facteurs supplémentaires qui ne sont pas necessaires a l etablissemen de l hypersensibilite de type bactérien Un fait est encore à re enir de cette maladie (agammaglobulinémie) realisant une veritable experience naturelle l atteinte elective de la formation des plasmocytes cellules qui ne semblent pas intervenir dans l hypersensibilite de type bacterien mais qui ont peut etre quelque chose a faire avec le rejet des homogreffes

Si bien que l on n est pas en droit de considérer a l heure actuelle que la reaction immunologique qui aboutit au rejet d un homogreffon peut être assimilee à une reaction d hypersensibilite de type retarde bacterien (Voisin 156)

Il nous semble meme qu il s agit là en fait d un faux probleme Il est bien naturel, lorsqu un nouveau phenomène est decouvert, de chercher a le rapporter a d autre phenomenes déja connus Il arrive cependant qu un tel rapprochement soit trop hâtif et que d autre part ces phenomènes déjà connus soient incompletement expliques Un tel rapprochement s il est trop rigide risque alor [illegible] du phénomene nouveau Il faut alors analy [illegible] es

[illegible] Il n est [illegible] orter des lumieres re arde bactérien [illegible] mes immuno [illegible] rne le phénomene

logiques Il semble que ce soit déjà le cas [illegible] de la tolerance spécifique acquise

Dans ces conditions il convient de regrouper les faits observes sous le titre d *hypersensibilité « de type homogreffe »* (156) et d essayer d analyser le role respectif que jouent les facteurs d origine cellulaire et les facteurs d origine sérique dans son etablissement et dans ses consequences

B Analyse de l hypersensibilité « de type homogreffe »

Toute analyse objective de la nature de l hypersensibilite « de type homogreffe » doit tenir compte des deux considerations suivantes *Le greffon est un tissu ou un organe tres complexe qui n est en rien comparable a un simple antigene ou meme à un organisme bactérien* par ailleurs l experience montre que *cellules et sérums semblent bien jouer tous deux un rôle dans le rejet des homogreffes*

1° Du fait de la complexite du greffon on est oblige d admettre que les antigenes liberés sont multiples et que d autre part le greffon lui meme est capable de réactions biologiques propres

Multiplicité des antigenes libérés par le greffon — Ces multiples antigenes doivent entrainer des réponses complexes de la part du receveur telles que reactions cellulaires formation d anticorps seriques et éventuellement formation d hypothetiques anticorps dits sessiles Ces differentes reactions jouent certainement un role tres inegal dans le rejet du greffon Il est possible qu il existe plusieurs systemes antigene anticorps susceptibles de jouer un role actif dans ce rejet c est d ailleurs une des manieres d expliquer la necessité d injection de cellules totales vivantes pour entrainer la tolerance specifique acquise alors que l on peut induire l etat inverse d immunité a moindres frais Il est vraisemblable que certains des systemes antigene anticorps que l on peut ou que l on pourra detecter ne jouent qu un role mineur dans le rejet du greffon Enfin certains jouent meme un role protecteur comme cela est etabli au moins dans le cas des homogreffes de tissus tumoraux (51 a 59) Et en effet un exemple très extraordinaire de la variete et de l antagonisme possible des systemes antigene anticorps rencontres dans l etude des reactions a l homogreffe est précisement fourni par le cas des homogreffes de tissus tumoraux Une telle greffe est en effet capable d entrainer l *immunisation* vis à vis d une deuxième greffe meme du donneur l immunite ainsi obtenue est transferable par les cellules et elle est de duree assez courte (quelques semaines au plus) La meme greffe entraine egalement la « facilitation » (phenomène XYZ de Casey ou enhancement phenomenon de Snell et Kaliss) vis à vis d une deuxième greffe du meme donneur cette facilitation » immunologique est transferable par le sérum et elle est de duree prolongee (plusieurs mois) Ceci est un argument de plus montrant que la multiplicité des reactions qui prennent place empeche toute assimilation de ces phenomènes a une reaction d hypersensibilite d un type simple Un nouvel argument est fourni par les réactions possibles du greffon lui meme (18 34 76 à 78 157)

Réactions propres du greffon — Le greffon est en effet capable de réactions dont les bactéries sont bien incapables Ces réactions concernent comme nous l avons vu (3 4 14 35) l activité mitotique des cellules epithéliales (158) les phenomenes vasculaires (2 3 9) et le tissu mésenchymateux lui meme C est peut etre cette dernière réaction qui est la plus curieuse le

greffon surtout lorsqu il s agit d un organe complexe comme le rein semble capable de réagir en donnant naissance a des plasmocytes C est en constatant la présence de cellules pyroninophiles que Simonsen (34) et Dempster (33 157) eurent l idée d'une reaction possible du greffon contre le receveur symetrique de la réaction inverse et contribuant peut etre pour sa part a entrainer l incompatibilité du receveur et du greffon qui aboutit au rejet du greffon Cette possibilité qui s est confirmée avec eclat dans le cas particulier de la tolérance acquise au greffon (Simonsen, 76 77 et Billingham 18 78) est un nouveau facteur de complexité qui appartient en propre a l immunologie des homogreffes

2° La deuxieme considération concerne le fait que cellules et serum semblent bien jouer tous deux un role actif dans le rejet des homogreffes *Rôle primordial des cellules et cellules en cause* — Sans revenir sur tout ce qui a ete dit concernant le role des cellules du receveur (cellules ganglionnaires 27 28 40 41 ou spléniques 27 28 40 41 ou meme d exsudat péritoneal 27 28) bornons nous à rappeler le caractère habituellement indispensable de leur intervention survie du greffon placé à l abri des cellules (chambre anterieure de l œil ou chambre a millipore) et transfert « adoptif » de l immunite (ou hypersensibilité) au greffon par le moyen des cellules Certaines experiences sont en outre de nature a fournir quelque renseignement *sur la nature des cellules en cause* *nous avons* vu que les sujets agammaglobulinemiques qui acceptent les homogreffes sont incapables de développer des cellules a caractere plasmocytaire (155) De leur coté Scothorne et Mac Gregor (159) ont constaté que le ganglion drainant la region du greffon (ce ganglion est precisément celui qui contient le plus de cellules capables de transferer « adoptivement » l hypersensibilite au greffon comme l a montre Mitchison) (131) subissait des modifications caracteristiques non observees en cas d autogreffes Ces modifications consistent en l apparition de « grandes cellules lymphoides » à nucleole très basophile et à cytoplasme également basophile et pyroninophile La morphologie de ces cellules est très comparable à celle des cellules generalement considérées comme productrices d anticorps et comme précurseurs des plasmocytes mûrs (160 a 164) De plus Scothorne (165 166) confirmant la prolongation de survie de l homogreffe suivant un traitement local ou général à la cortisone (déjà observee par Billingham Krohn et Medawar 167 168) a vu que cette prolongation de survie allait de pair avec une suppression presque complete d apparition des cellules de ce type dans le ganglion correspondant *Il y a là un ensemble de faits qui ont certainement* une signification importante

Rôle eventuel du serum — Par ailleurs le sérum du receveur joue un role certain mais la question est de savoir si les facteurs actifs qu il contient ont la signification de cofacteurs non spécifiques aidant à l action des cellules immunes ou bien s ils représentent des facteurs specifiques avant la signification d anticorps

En faveur d un role non specifique du serum (cofacteur) sont les experiences de Weaver Algire et Prehn (134) qui ont constate que des cellules immunes (provenant de la rate d animaux sensibilisés par une greffe) sont capables de lyser des cellules du receveur si ces deux types de cellules sont

placés dans une chambre à diffusion (perméable seulement au sérum). Cette lyse est observée lorsque les chambres sont placées dans un animal (il s'agit ici de souris) de même lignée pure que celui dont proviennent les cellules immunes et ce même si cet hôte n'est pas lui-même immunisé contre le receveur. Il semble bien que cet hôte fournisse quelque facteur sérique non spécifique nécessaire à la lyse car celle-ci ne s'observe pas « in vitro » (128, 134).

Mais il existe d'autre part un faisceau de données expérimentales dont le nombre va croissant, montrant le caractère souvent spécifique du rôle du sérum. Dans certains cas exceptionnels le sérum peut même suffire à entraîner la mort du greffon (27, 28, 119). Nous avons vu que le sérum du receveur peut contenir des « anticorps » toxiques pour les cellules du greffon soit dans la combinaison utilisant successivement les deux étapes « in vitro in vivo » [greffe de tissus cancéreux (139, 142) ou même normaux (31)] soit même directement par injection « in vivo » (greffe de leucémie chez la souris) (130).

Par ailleurs avec P. Maurer nous avons montré (27, 28) que des anti-sérums étaient capables, à eux seuls, d'entraîner le rejet d'un greffon : rejet d'un autogreffon par action d'un sérum hétérologue (non spécifique de l'individu donneur, mais anti-espèce ou anti-organe) ; rejet accéléré d'un iso-greffon par action d'un sérum hétérologue (spécifique de l'individu donneur ou simplement anti-espèce ou anti-organe) ; rejet accéléré d'un iso-greffon par action d'un sérum homologue spécifique de l'individu donneur ; rejet d'un auto-greffon chez des animaux présentant une atteinte cutanée attribuée à des anticorps anti-peau (169) (il s'agirait alors de l'action d'anti-corps anti-organe). Quelle qu'ait été, dans ces expériences, la spécificité des anticorps (anti-individu, anti-organe ou anti-espèce), elles apportent la preuve que des anticorps sériques peuvent suffire à entraîner le rejet rapide d'un greffon.

Stetson et Demopoulos (119) enfin ont récemment confirmé et étendu certaines de ces dernières expériences : ils immunisent un animal futur receveur d'une greffe de peau en lui injectant des cellules spléniques du futur donneur de peau, incorporées dans des substances adjuvantes. Le degré d'immunité au greffon est assez intense pour entraîner le phénomène de la « greffe blanche ». Ce phénomène peut être transféré passivement chez un receveur neuf par le moyen du sérum de l'animal immunisé. Ce même sérum, injecté localement autour d'une greffe du même donneur chez un autre receveur neuf, entraîne un rejet rapide et spécifique de l'homogreffe.

Ainsi le rôle du sérum et des anticorps circulants semble s'avérer de moins en moins négligeable et même important.

3° S'il fallait à tout prix tirer des faits et considérations précédents une conclusion provisoire concernant la nature des phénomènes immunologiques responsables de l'hypersensibilité « de type homogreffe » nous proposerions l'interprétation que nous avions déjà suggérée (28) à savoir que les anticorps en cause sont, d'une manière ou d'une autre, liés aux cellules lymphoïdes et que, dans certaines conditions non précisées, ils peuvent être libérés et passer dans le sérum. Cette interprétation pouvant être complétée de la manière suivante : 1° Une concentration cellulaire locale au niveau du lit du greffon et dans le greffon lui-même permettrait une concen

tration en anticorps bien supérieure a celle existant dans le serum surtout si l on invoque une formation locale d anticorps (lit du greffon) (119) 2° Les cellules contenant et libérant des anticorps pourraient bien etre des plasmocytes (ou des cellules pyroninophiles précurseurs de plasmocytes) 3° Il n est pas impossible que plusieurs systemes antigène anticorps aient un role actif à jouer dans le rejet ou le retard apporte au rejet de l homogreffe alors que d autres ne jouent peut etre qu un role minime 4° La réaction inverse du greffon contre le receveur, n est peut être pas à négliger dans le deroulement des phénomenes locaux qui aboutissent au rejet et à la mort de l homogreffe (34 157)

Cependant de telles conclusions ne sauraient etre que provisoires car les donnees experimentales ne sont pas encore assez nombreuses pour permettre de proposer des interprétations qui soient plus que des hypothèses de travail

VII MÉCANISME INTIME DU REJET ET DE LA MORT DU GREFFON

Le caractere encore incomplet de nos connaissances empeche égalem nt de donner une interprétation coherente et précise des faits histologiques observes au cours de l evolution et de la mort d une homogreffe C est ce qui rend compte de la brieveté de ce dernier chapitre

Parmi les faits histologiques on est autorisé a considerer comme significatifs ceux qui sont observés au cours de l evolution des homogreffes de premier ou de second set ou meme de sets multiples (première ou deuxieme greffe ou greffes suivantes d un meme donneur à un meme receveur) e qui sont ab ents au cours de l evolution des autogreffes

Au cours de l evolution d une première homogreffe (3 14) de peau on est frappé par trois faits l abondance des infiltrats périvasculaires a noyaux ronds l arret des mitoses de la couche malpighienne apres une prolifration assez intense vers le 7e jour et enfin la thrombose des vaisseaux avec suffusions hemorragiques qui debute vers le 8e jour L examen de la greffe in situ au microcapillaroscope (2) précise le comportement dynamique et l evolution des vaisseaux apres une revascularisation avec rétablissement d un courant sanguin precoce (commençant le 2e jour et ach vee le 4e jour) le debut de la « réaction de rejet » est très precoce des le 5e jour la vasodilatation généralisee du greffon annonce une stase vasculaire qui survient le lendemain bientot suivie (environ vingt quatre heures après) par des thromboses et suffusions hémorragiques

Au cours de l evolution d une deuxieme homogreffe (3 14) de peau du meme donneur au meme receveur on observe par rapport à la précédente evolution les modifications suivantes infiltrats perivasculaires plus importants absence de mitoses dans la couche malpighienne (158) survenue plus rapide des altérations vasculaires

Enfin au cours de l evolution de greffes successives du meme donneur (15) (comme au cours de l hyperimmunisation « artificielle » 37 119) un fait nouveau peut apparaitre l absence complete de vascularisation

Ainsi les phénomènes et altérations vasculaires semblent dominer la scene, mais cons ituent ils une cause ou une consequence du rejet de

l homogreffon ? En d autres termes la reaction immunologique du receveur fait elle sentir ses effets primitivement sur les vaisseaux du greffon avec mort consecutive de ce dernier ou bien les vaisseaux sont ils touches secondairement a l atteinte des tissus extravasculaires du greffon ? Il semble bien que l ischémie entrainee par l arret de la circulation n ait pas un role très important dans la mort du greffon car on sait que la phase de vascularisation du greffon est precédee d une phase avasculaire pendant laquelle le greffon survit tres bien qu il s agisse d une autogreffe ou d une homogreffe Cette phase avasculaire peut etre prolongee parfois plus d une dizaine de jours [illegible]

veur Les thromboses et suffusions hemorragiques ont pour consequence de hater la mort des autres elements du greffon car elles offrent un acces plus rapide des élements antagonistes aux tissus extravasculaires du greffon L evolution des modifications concernant l epithelium malpighien de revetement ou l epithelium glandulaire et des follicules pileux est suivie avec plus de precision que celle des tissus mesenchymateux extravasculaires car au niveau de ces derniers se pose tres souvent la question de l origine (greffon ou receveur) des cellules observees

En definitive il est bien evident qu une comprehension precise des mecanismes intimes du rejet et de la mort du greffon necessite la solution des problemes concernant la nature des antigenes et des anticorps qui sont a l origine de ce rejet et de cette mortification

RÉSUMÉ

Le présent rapport traitant du probleme immunologique des homogreffes comporte sept chapitres

Au cours du premier chapitre est expose le deroulement des faits qui aboutissent au rejet des homogreffes et sont resumées les theories qui ont tente de donner une interpretation biologique a ce rejet inéluctable

Le deuxieme chapitre apporte de nombreux arguments en faveur de la theorie d une reaction immunitaire d apres laquelle le receveur agirait vis a vis du greffon comme vis à vis d un antigene etranger par une reaction immunologique spécifique

Le troisième chapitre resume les objections qui peuvent etre faites a cette theorie et qui relevent pour la plupart d interpretations incompletes de faits particuliers

Le quatrieme chapitre apporte des arguments definitifs levant ces objections et residant en la possibilite d entrainer a volonte chez le receveur une sensibilisation ou une désensibilisation (partielle ou totale) spécifique du greffon — ce qui aboutit a une diminution ou a une augmentation (temporaire ou definitive) du temps de survie de l homogreffon — et ce par des moyens d ordre immunologique

Le cinquieme chapitre est consacre à étudier la nature des antigenes en

cause. Les principaux renseignements sont obtenus par l'analyse des deux phénomènes suivants : ces antigènes ne semblent présents que dans des cellules vivantes (au moins pour entraîner la désensibilisation spécifique) et ils sont spécifiques d'individu. Tous deux tendent à localiser les antigènes en cause au niveau des mécanismes de synthèse protéique.

Au cours du sixième chapitre sont passés en revue les arguments tendant [illegible] d'hypersens-

l'hypersensibilité « de type homogreffe ». Une telle analyse conduit à la notion que les anticorps sériques et les plasmocytes jouent peut-être dans le rejet du greffon un rôle plus important qu'on ne le croit généralement.

Le septième chapitre enfin montre que la connaissance du mécanisme ultime du rejet et de la mort du greffon dépend des progrès qui seront faits dans la connaissance des antigènes en cause et des « anticorps » responsables, progrès qui permettront d'établir avec précision les rapports liant les réactions immunologiques et les constatations histologiques.

C'est à l'immunologie que nous devons nos connaissances, nos possibilités d'action et nos espoirs dans le domaine des homogreffes. Nous savons en effet aujourd'hui que la signification du rejet des homogreffes est celle d'une réaction de nature immunologique ; nous pouvons au laboratoire abréger ou prolonger à volonté la survie d'une homogreffe et nous espérons qu'un jour il sera possible de donner à ces recherches une application pratique. C'est dans le domaine immunologique que se jouera, que se joue déjà la partie passionnante dont l'enjeu est la possibilité de pratiquer des homotransplantations d'organes vitaux assurés d'une survie définitive.

SUMMARY

This report deals with the immunological problem of homografts and is divided into seven parts.

I. — The sequence of events leading to the rejection of homografts is reviewed as well as the theories trying to explain biologically this unavoidable rejection.

II. — Numerous facts are presented in favour of the theory according to which *the recipient should act with respect to the graft* as towards a foreign antigen : thus an immunological response is setting in.

III. — The objections that may be raised against this theory are summed up. Most of them can be ascribed to incomplete interpretation or to the recording of isolated facts.

IV. — Final arguments are brought forward to dispose of these objections. They consist of the ability to bring about willingly by immunological means the graft's specific sensitization or desensitization (either partial or total) and thus to obtain either a shortening or a prolongation (permanent or transitory) of the homograft's time of survival.

V — The nature of the antigens involved is studied The main evidence is drawn from the following facts

This antigens only appear in living cells at least to bring about specific desensitization and seem to be individual specific

Those two facts tend towards a localization of the involved antigens on the level of the the mechanisms of protein synthesis

VI — Arguments tending to integrate the homograft s hypersensitivity with already known types of hypersensitivity such as the immediate (ana phylactic or the delayed (bacterial) type are reviewed

It is suggested that the real problem lies in the objective analysis of the phenomena responsible for the hypersensitization of the homograft type Such an analysis is leading to the sugge tion that antibodies may play a larger part than commonly believed in the process of the graft rejection

VII — To conclude the author points out that the understanding of the final mechanism of the graft s rejection and d ath are in close connection with the progress that will be made in this field towards a more complete knowledge of the antigens and antibodies involved This progress will enable us to ascertain the relation which links immunological reactions to histolo gical observations

In the field of homografts we owe to immunology our attainments our possibilities and our hopes

In fact we know to day that the rejection of the homog raft meansan exis ting immunological response

In the course of laboratory experiments we are able at will to shorten or to extend the survival of an homograft and hope to give some day a practical application to our researches

This thrilling game will be played out in the fields of immunology it s stakes are the possibilities of performing homotransplantations of vital organs and of ensuring their undefinit survival

ZUSAMMENFASSUNG

Der vorliegende Bericht der das Problem der Immunitatsforschung behandelt enthalt sieben Kapitel

— *Im Laufe des ersten Kapitels* wird die Abwicklung der Tatsachen dargestellt die auf eine Nichtannahme der Homoplastik hinauslaufen Es werden die Theorien zusammengefaßt die eine biologische Interpreta tion dieser unvermeidlichen Abweisung nahe legen

— *Das zweite Kapitel* sammelt zahlreiche Argumente zu Gunsten einer immunitaren Reaktion nach welcher der Empfanger dem Transplantat gegenuber so reagiert wie gegenuber einem fremden Antigen durch eine spezifische immunitare Reaktion

— *Das dritte Kapitel* faßt die Einwande zusammen die gegen diese Theorie eingewendet werden konnen und die zum großen Teil unvollstan dige Interpretationen von besonderen Erscheinungen angeben

— *Das vierte Kapitel* gibt definitive Beweise die diese Einwande hinfallig machen und die in der [illegible]

nach Belieben eine dem Transplantaten eigene Sensibilität oder Desensibilität zu bewirken — was auf eine Verringerung oder Steigerung (zeitweise oder definitif) der Dauer des Weiterlebens des Transplantaten hinausläuft und dieses durch Mittel die der Immunitätsforschung angehören

— *Das fünfte Kapitel* ist dem Studium der Natur der in Frage kommenden Antigene gewidmet Die hauptsächlichen Nachweise werden durch Analysen der beiden folgenden Erscheinungen erbracht Diese Antigene scheinen nur in lebenden Zellen vorhanden zu sein (zumindest um die spezifische Desensibilität hervorzurufen) sie sind Spezifika des Einzelwesens Alle beide zielen auf eine Lokalisierung der in Frage kommenden Antigene hin auf der Bassis der Mechanismen von Proteinsynthesen

— *Im Laufe des sechsten Kapitels* werden die Argumente geprüft die darauf zielen die Hypersensibilität dem Homotransplantaten gegenüber an einen Typus der Hypersensibilität den wir schon kennen anzugleichen (Hypersensibilität mit sofortiger anaphylaktischer Wirkung und Hyper sensibilität mit verspäteter oder bakterieller Wirkung) Es wird nahe gelegt, daß das wahre Problem darin besteht die Erscheinungen die für die Hypersensibilität des homoplastischen Typus verantwortlich sind, objektiv zu analysieren Eine solche Analyse führt zu der Beobachtung daß die Abwehrstoffe des Serums und die Plasmatiken vielleicht bei der Über tragung der Transplantaten eine größere Rolle spielen als man es bis her laufend angenommen hat

— *Das siebente Kapitel* zeigt schließlich daß die Kenntnis über den letzten Mechanismus der Nichtannahme und des Todes des Transplantaten von den Fortschritten abhängig ist die in Hinblick auf die Kenntnis der in Frage kommenden Antigene und der verantwortlichen „Antikörper gemacht werden E werden Fortschritte sein die erlauben die Beziehungen welche die immunologischen Reaktionen und die histologischen Fest stellungen verbinden mit Sicherheit und Genauigkeit festzulegen

Der Immunitätslehre verdanken wir unsere Kenntnisse Handlungs möglichkeiten und unsere Hoffnungen auf dem Gebiet der Transplantation Tatsächlich wissen wir heute daß die Abweisung des Transplantaten die Bedeutung einer Reaktion von Immunologischer Natur ist Wir können im Laboratorium das Weiterleben einer Homoplastik nach Belieben verlän gern oder verkürzen und wir hoffen daß es uns eines Tages möglich sein wird diesen Forschungen eine praktische Anwendung zu geben Auf dem Gebiete der Immunologie zeichnet sich schon das leidenschaftliche Spiel ab de sen Einsatz die Möglichkeit bedeutet die Homotransplan tation von lebenden Organen mit definitiv gesichertem Weiterleben prak tisch anzuwenden

RESUMEN

La presente comunicación que se refiere al aspecto inmunológico de los homoinjertos consta de siete capítulos

El el *primer* capítulo se expone la sucesión de hechos que conducen a la expulsión de los homoinjertos y se resumen las teorías que han ensayado de dar una interpretacion biológica a esta expulsión

En el *segundo* capítulo se exponen los argumentos en favor de la teoría que supone que se trata de una reaccion inmunitaria segun la cual el sujeto

receptor actuaría frente a los injertos de la misma manera que frente a un antígeno extraño es decir por una reaccion immunologica especifica

El *tercer* capítulo está consagrado a enumerar las objeciones que se han presentado a esta teoría y que traducen en su mayor parte intepretaciones incompletas de hechos aislados

En el *cuarto* capítulo se aportan argumentos definitivos que levantan esas objeciones basados en la posibilidad de producir a voluntad una sensibilización o desensibilización parcial o total del receptor especifica al injerto De esta manera y por medios de naturaleza inmunologica se consigue un aumento o una disminucion temporaria o definitiva del tiempo de vida del injerto

El *quinto* capítulo está dedicado a estudiar *la naturaleza* de los antigenos responsables *Las principales indicationes resultan del análisis de los dos* fenómenos *siguientes estos antigenos parecen existir solamente en las* células *vivas (al menos para provocar la desensibilizacion especifica)* y son especificos *del individuo Estas comprobaciones hacen presumir* que los antigenos deben estar vinculados con los mecanismos de síntesis proteica

En el capitulo *sexto* se señalan los argumentos que tratan de asimilar la hipersensibilidad al homoinjerto con los tipos ya conocidos (inmediato o tardivo) y se sugiere que el verdadero problema consiste en analizar objetiva mente los fenomenos responsables de la hipersensibilidad de tipo injerto Tal análisis indica que los anticuerpos séricos y los plasmocitos desempenan un papel más importante del que generalmente se les asigna

Finalmente en el *septimo* capitulo se hace notar que el conocimiento del mecanismo que determina la expulsion y muerte del injerto depende de los progresos que se realicen en el estudio de los antígenos y anticuerpos responsables progresos que permitirán establecer con precision las rela ciones entre las reacciones inmunológicas y los hallazgos histológicos

Nuestros conocimientos nuestras posibilidades de acción y nuestras esperanzas en el dominio de los homoinjertos les debemos a la Inmunología Sabemos en efecto que el fenomeno de expulsión es de naturaleza *inmuno lógica* podemos en el laboratorio acortar *o alargar* a voluntad *la vida de* un injerto y *esperamos* que un día sera posible dar a estas investigaciones una aplicacion practica *Es en el terreno inmunológico* donde se jugara que se está jugando ya la partida pasionante cuyo premio es la posibilidad de practicar homotransplantes de órganos vitales con supervivencia definitiva asegurada

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nach Belieben eine dem Transplantaten eigene Sensibilität oder Desensibilität zu bewirken — was auf eine Verringerung oder Steigerung (zeitweise oder definitif) der Dauer des Weiterlebens des Transplantaten hinausläuft und dieses durch Mittel die der Immunitätsforschung angehören

— *Das fünfte Kapitel* ist dem Studium der Natur der in Frage kommenden Antigene gewidmet Die hauptsächlichen Nachweise werden durch Analysen der beiden folgenden Erscheinungen erbracht Diese Antigene scheinen nur in lebenden *Zellen* vorhanden zu sein (zumindest *um die spezifische* Desensibilität hervorzurufen) sie sind Spezifika des Einzelwesens Alle beide zielen auf eine Lokalisierung der in Frage kommenden Antigene hin auf der Bassis der Mechanismen von Proteinsynthesen

— *Im Laufe des sechsten Kapitels* werden die Argumente geprüft die darauf zielen die Hypersensibilität dem Homotransplantaten gegenüber an einen Typus der Hypersensibilität den wir schon kennen anzugleichen (Hypersensibilität mit sofortiger anaphylaktischer Wirkung und Hypersensibilität mit verspäteter oder bakterieller Wirkung) Es wird nahe gelegt, daß das wahre Problem darin besteht die Erscheinungen die für die *Hypersensibilität des homoplastischen Typus* verantwortlich sind objektiv zu analysieren Eine solche Analyse führt zu der Beobachtung daß die Abwehrstoffe des Serums und die Plasmatiken vielleicht bei der Übertragung der Transplantaten eine größere Rolle spielen als man es bisher laufend angenommen hat

— *Das siebente Kapitel* zeigt schließlich daß die Kenntnis über den letzten Mechanismus der Nichtannahme und des Todes des Transplantaten von den Fortschritten abhängig ist die in Hinblick auf die Kenntnis der in Frage kommenden Antigene und der verantwortlichen Antikörper gemacht werden Es werden Fortschritte sein die erlauben die Beziehungen welche die immunologischen Reaktionen und die histologischen Feststellungen verbinden mit Sicherheit und Genauigkeit festzulegen

Der Immunitätslehre verdanken wir unsere Kenntnisse Handlungsmöglichkeiten und unsere Hoffnungen auf dem Gebiet der Transplantation. Tatsächlich wissen wir heute daß die Abweisung des Transplantaten die Bedeutung einer Reaktion von Immunologischer Natur ist Wir können im Laboratorium das Weiterleben einer Homoplastik nach Belieben verlängern oder verkürzen und wir hoffen daß es uns eines Tages möglich sein wird diesen Forschungen eine praktische Anwendung zu geben Auf dem Gebiete der Immunologie zeichnet sich schon das leidenschaftliche Spiel ab dessen Einsatz die Möglichkeit bedeutet die Homotransplantation von lebenden Organen mit definitiv gesichertem Weiterleben praktisch anzuwenden

RESUMEN

La presente comunicación que se refiere al aspecto inmunológico de los homoinjertos consta de siete capítulos

El el *primer* capítulo se expone la sucesión de hechos que conducen a la expulsión de los homoinjertos y se resumen las teorías que han ensayado de dar una interpretación biológica a esta expulsión

En el *segundo* capítulo se exponen los argumentos en favor de la teoría que supone que se trata de una reacción inmunitaria según la cual el sujeto

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SYMPOSIUM VI

L'eczéma diathésique
Atopic dermatitis
Atopische dermatitis
El eczema diatestico

ÉVOLUTION ET ASPECT CLINIQUE DES DERMATOSES ATOPIQUES

par

W JADASSOHN

(Clinique Universitaire de Dermatologie Geneve)

Lorsque le Dr Sulzberger «moderator» de ce Symposium m a demande d introduire «the topic by general remarks of 10 minutes» sur le sujet Course and clinical aspect j ai prie me collaborateurs Musso Hunziker et Brun d activer leurs experiences en cours concernant cette affection L equipe chargee de ce travail me parait assez qualifiee pour entreprendre de telles recherches Musso est specialiste de medecine interne il possede une bonne formation dermatologique et s interesse beaucoup a l allergie Hunziker est dermatologue et Brun est chimiste et chef de laboratoire de la clinique Tous trois font partie du staff de la Clinique Dermatologique depuis des annees Ils sont loin d avoir termine leurs experiences mais ils ont toutefois deja obtenu quelques resultats et je voudrais leur laisser l honneur de vous les presenter Pour ma part je me restreindrai a quelques breves remarques générales

1° A mon avis l evolution de l eczema infantile «atopic infantile eczema» dans les semaines et mois qui suivent l apparition de la dermatose depend en tout premier lieu du traitement local institue La creme a l hydrocortisone peut rendre de grands services mais ce seul traitement meme si l on ne tient pas compte du prix eleve est souvent nettement insuffisant Les vieux traitements tels que les compresses d eau boriquee de nitrate d argent etc sont la plupart du temps indispensables L oleate d argent en suspension aqueuse est de grande utilite de meme que certaines pommades pommade au vioforme vaselinum adustum tumenol ou les teintures badigeons et le goudron etc Autant que possible le traitement est entrepris a la Clinique Dermatologique Mais ce n est au fond pas du traitement dont je suis charge de vous entretenir je dois vous parler de l evolution de la maladie

En ce qui concerne cette dernière il est tres important de ne pas se contenter uniquement de traiter l enfant et de le blanchir il faut enseigner le traitement a la mere Il est necessaire qu elle vienne a la clinique pour qu elle puisse se rendre compte de quelle maniere les infirmieres traitent l enfant

On doit lui enseigner le traitement d entretien et lui expliquer tout ce qui est à eviter pour parer a une rechute Les parents doivent etre à meme de soigner une petite rechute avant que l affection devienne importante De temps à autre nous revoyons d anciens petits malades dont l etat cutane est excellent les parents toutefois, rapportent que s ils ne font pas continuellement un traitement local la peau se pejore Parmi les produits que nous avons prescrits ce n est pas toujours l hydrocortisone qu ils choisissent et selon leur expérience ils lui preferent souvent des produits colores bien que ceux ci soient d emploi beaucoup plus desagreable

2° L eczema infantile peut disparaitre completement mais il peut aussi evoluer en nevrodermite il arrive aussi que de l asthme apparaisse combine ou non avec les lesions de la peau Le nombre de cas d eczema infantile que nous avons pu controler apres des années est trop restreint pour que nous puissions tirer des conclusions certaines Nous nous efforçons cependant d examiner le plus de cas possible et maintenant deja (fevrier 1958) toutes les possibilites citees plus haut ont ete constatees Mes collaborateurs vous en donneront les details dans leurs communications

3° J ai frequemment souligne que la réaction au blanc d œuf — introduite par Rackemann Moro et coll — ne nous semble pas avoir la moindre valeur étiologique Mais il est certain qu elle presente un grand interet non seulement théorique mais également diagnostique bien que nous doutions que cette reaction soit positive dans 100 % de cas d eczema infantile Apres l âge de deux ans apres la guerison plus ou moins complete de la dermatose ou lorsqu elle prend l aspect de l *atopic dermatitis* des adultes (nevrodermite) la reaction au blanc d œuf se negative dans la grande majorite des cas

4° Brun a fabrique un allergène de poussière purifie qui contient surtout la fraction des polysaccharides Mes collaborateurs l ont très fortement dilue (1/100 000) et ont evité de cette maniere des reactions chez les temoins reactions que l on constate souvent avec d autres antigenes de poussiere Je vous renvoie a la communication de Musso Hunziker et Brun et je la resume uniquement la reaction obtenue avec notre antigène poussiere est presque toujours positive chez les petits enfants lorsque la réaction au blanc d œuf est elle meme positive Elle devient negative lorsque l enfant grandit et lorsque la reaction au blanc d œuf se négative Nous ne possedons pas encore suffisamment d enfants atteints de nevrodermite et de personnes souffrant de nevrodermite circonscrite pour nous prononcer sur les resultats obtenus avec notre allergene poussiere Chez l adulte souffrant de nevrodermite disseminee *(atopic dermatitis disseminata)* la reaction est positive dans la tres grande majorite des cas Il en est de meme pour l asthme et le rhume des foins

5° En ce qui concerne l evolution de la névrodermite disséminee de adultes *(atopic dermatitis disseminata)* le traitement local me semble aussi tres important Tout ce que j ai dit pour l eczéma infantile est valable *mutatis mutandis* pour cette forme d atopie de l adulte Le malade doit devenir son propre dermatologiste Les derivés de la cortisone facilitent grandement l introduction du traitement local mais ils ne peuvent le remplacer vu que ces hormones ne peuvent etre administrees a des doses considerables pendant une longue periode Le traitement aux rayons X execute prudemment n a rien perdu de sa valeur bien au contraire et depuis que grâce a la fenetre

de beryllium nous pouvons l'appliquer d'une manière très étendue sans avoir à craindre des réactions générales, il a encore pris plus d'importance.

6° Les questions d'ordre psychologique jouent sans aucun doute un grand rôle dans l'évolution de l'*atopic dermatitis disseminata* des adultes. Je crois, du point de vue psychologique, qu'il est très important que le malade ait pu se rendre compte de l'utilité du traitement local et qu'il sache qu'il peut l'appliquer lui-même immédiatement si le besoin s'en fait sentir. En outre, il est nécessaire qu'il sache ce qu'il doit ou ne doit pas faire pour maintenir sa peau dans un état aussi satisfaisant que possible.

7° Pour de très divers motifs il me semble que l'on a eu raison d'introduire le terme d'atopie et d'avoir ainsi rapproché en premier lieu l'eczéma infantile, la névrodermite disséminée et l'asthme. Parmi ces motifs, je pense au test à la poussière — surtout celui pratiqué avec l'allergène poussière de Musso, Hunziker et Brun qui, je crois, joue un rôle important. Le rhume des foins me semble tout aussi faire encore de juste... partie de ce groupe de l'atopie, notamment parce que Musso a constaté que les réactions à la poussière effectuées avec notre allergène sont très fréquemment positives dans cette affection. Par contre, je ne peux pas encore me prononcer sur la classification de la névrodermite circonscrite *(lichen vidal circumscriptus)*.

8° La réaction au blanc d'œuf n'est certainement pas une réaction caractéristique pour l'atopie car elle n'est pratiquement positive que dans l'eczéma infantile. La réaction avec notre antigène de poussière semble être régulièrement positive dans l'eczéma infantile, la névrodermite disséminée des adultes, l'asthme et le rhume des foins. Avant de parler définitivement d'un *test pour l'atopie*, nous devrons encore augmenter notre matériel bien qu'il soit déjà considérable.

Vous pourriez me reprocher d'avoir interprété le sujet « clinique et évolution des dermatoses atopiques » par trop largement. Je m'en excuse, mais je n'ai pas voulu vous décrire le tableau clinique de ces dermatoses que vous connaissez tous. Quant à leur évolution, elle dépend en grande partie de ce qu'on entreprend pour influencer la maladie. Je vous ai donné mes opinions personnelles. Il m'a semblé que cette manière de faire était indiquée car c'est de cette façon qu'on déclenche une discussion.

Les résultats qui sont à la base d'un « test pour l'atopie » vous seront communiqués par Musso, Brun et Hunziker.

RÉSUMÉ

L'auteur fait quelques remarques concernant les sujets suivants :

— Importance du traitement local sur l'évolution de l'eczéma infantile.

— Apparition de névrodermite disséminée ou d'asthme après eczéma infantile.

— Test au blanc d'œuf.

— Test pour déceler l'atopie (test avec un allergène de poussière contenant la fraction des polysaccharides).

— Importance du traitement local et des dérivés de la cortisone sur l'évolution de la névrodermite disséminée de l'adulte.

SUMMARY

The following problems are discussed
— Importance of local treatment on the course of atopic dermatitis in infants
— Appearance of disseminated neurodermatitis or asthma following infantile eczema
— Ovalbumin test
— Test for detecting atopy (test with dust containing polysaccharides fractions)
— Importance of local treatment and the use of the cortisone derivatives on the course of disseminated neurodermatitis in adults

ZUSAMMENFASSUNG

Der Autor wird über folgende Probleme sprechen
— Bedeutung der lokalen Behandlung für die Entwicklung des infantilen Ekzems
— Auftreten einer disseminierten Neurodermitis oder Asthmas nach dem infantilen Ekzem
— Test auf Eiweiss
— Test um die Atopie aufzudecken (Test mit einem Stauballergen das Fraktionen der Polysaccharide enthält)
— Bedeutung der Lokaltherapie und der Behandlung mit Cortison derivaten für die Entwicklung der disseminierten Neurodermitis beim Erwachsenen

RESUMEN

El autor se refiere a los siguientes aspectos
— Importancia del tratamiento local sobre la evolución del eczema infantil
— Aparición de neurodermitis o asma después del eczema infantil
— Prueba de la clara de huevo
— Prueba para investigar la atopia (con un alergeno de polvo doméstico que contenga la fracción polisacárida)
— Importancia del tratamiento local y de los derivados de la cortisona sobre la evolución de la neurodermitis en el adulto

KONSTITUTIONS-, UMWELT- UND KLIMAFAKTOREN BEI DER KONSTITUTIONELLEN NEURODERMITIS

von

Alfred MARCHIONINI, Siegfried BORELLI und Dorothee EICHHOFF
(Dermatologische Klinik und Poliklinik der Universität München)

Die konstitutionelle Neurodermitis beschäftigt unsere Forschung seit vielen Jahren. Abgesehen von der ätiopathogenetischen und therapeutischen Problematik ist es das Mitgefühl mit den in seelischer, körperlicher und sozialer Beziehung leidenden Kranken, das unser ständiges Interesse wach hält. Wenn die Lösung unserer ärztlichen Aufgabe bei dieser Krankheit derzeitig auch noch weit entfernt scheint, so kann man doch feststellen, daß im Verlaufe der letzten Jahrzehnte mancherlei Einzelbefunde erhoben wurden, die uns weitere Ansätze ermöglichen.

Die Träger nur weniger dermatologischer Krankheitsbilder weisen so zahlreiche charakteristische Eigentümlichkeiten (Stigmata) einer besonderen Konstitution auf wie die *Neurodermitis constitutionalis sive atopica*, eine Bezeichnung, die erst vor kurzem als Ergebnis gemeinsamer Untersuchungen und Überlegungen der Zürcher und Münchener Dermatologischen Kliniken vorgeschlagen wurde. Im Körperbau fällt das Überwiegen der Leptosomen bzw. Leptosom-athletischen auf (Myśliwiec und M. Soetbeer, Rost und Marchionini, Brill, Brandt, Spiethoff sowie Kochs). Anthropometrisch wiesen Borelli und Kraft nach, daß rund 61 % überwiegend leptosomen, 15,5 % athletischen Habitus zeigen (Abb. 1). Demgegenüber weist der normale europäische Bevölkerungsdurchschnitt einen Anteil der leptosomen und athletischen Proportionen in zusammen nur 40 bis 50 % der untersuchten Personen auf.

Außer im körperlichen Habitus ist eine Übereinstimmung im psychischen Bereich zu erkennen (M. Soetbeer und Myśliwiec, Kepecs, Rabin und Robin, Wittkower und Edgell, Borelli). Es besteht eine Bipolarität der Charakterstruktur im Sinne einer Spannung. Unter den Komponenten des Charaktergefüges zeigten der Verstandesanteil und der introvertierte Gefühlsanteil im allgemeinen die höchste Entwicklung. Zwischen den Tendenzen des Gefühls einerseits und denen des Verstandes bzw. denen des Willens läßt sich in besonders ausgeprägter und einheitlicher Weise bei diesem Kreis der Kranken eine Unausgeglichenheit und ein Spannungsge-

fühl feststellen. Abb. 2 gibt in schematischer Weise die Ausprägung der einzelnen Anteile des Charakters (der « Teilstrukturen ») sowie des Spannungsverlaufes entsprechend den Ergebnissen der Untersuchungen von Borelli an unserer Klinik wieder.

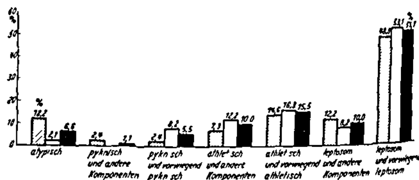


Abb. 1. Die Verteilung von 41 Hamburger, 49 Münchener, zusammen 90 Neurodermitiskranken auf die verschiedennn Konstitutionstypen zahlenmäßig, prozentual und graphisch dargestellt.
▨ Krankengut aus Hamburg
□ Krankengut aus München
■ Gesamtzahl der antropologisch gemessenen Neurodermitiskranken aus Hamburg und München zusammen

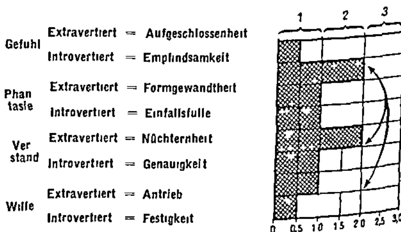


Abb. 2. *Schematische* Darstellung über die Ausprägung der verschiedenen Anteile des Charakters (Teilstrukturen) und der Spannungsverläufe zwischen diesen Strukturanteilen (nach BORELLI) (0,5, 1,0 bis 3,0 = Qualität der Ausbildung bzw. Differenzierung ⟷ = Verlauf der innercharakterlichen Spannung).

Zu der Bedeutung psychisch wirksamer Faktoren in der Ätiopathogenese der Neurodermitis nahmen mehrere Autoren in letzter Zeit erneut Stellung

Marmor Ashley Tabashnik Starkan und Mc Donald verweisen (1956) auf die Bedeutung der Mutter Kind Beziehung fur das Auftreten von Neurodermitisschuben und fur die Manifestation des Leidens Diese Autoren nennen die Trennung von der Mutter die Vernachlassigung rauhe bzw lieblose Behandlung Abwesenheit der Mutter infolge Berufstatigkeit elterliche Spannungen usw als Ursachen von Dauertraumen In gewisser Hinsicht sehen sie in der Auslosung der Krankheitssymptome den Ausdruck einer Adaptationsstorung die Reaktion auf eine seelische Überbeanspruchung im Sinne von Selye mit der Provokation einer seelischen Überempfindlichkeit Das gesamte Krankheitsgeschehen wird als Folge eines psychischen und physischen Stress angesehen

Fiske und Obermayer stellen ebenfalls (1954) die Bedeutung von Personlichkeit und emotionalen Faktoren in der Ätiologie der Neurodermitis heraus Nach ihren Beobachtungen handelt es sich bei Neurodermitiskranken — im Gegensatz zu anderen Hautkranken oder Neurotikern — um eine sehr homogene Menschengruppe Die Grundpersonlichkeit ist unausgeglichen infolge infantiler Strebungen Der Juckreiz habe Bedeutung hinsichtlich seiner exhibitionistischen selbstbestrafenden — masochistischen und erotischen Komponenten

Auch die gunstigen Ergebnisse der noch zu besprechenden Klimabehandlung werden bei Wirksamkeit auf solche seelischen Faktoren bezogen Smith und Garret (1953) sehen den Erfolg einer klimatischen Behandlung nicht in der Klimaveranderung allein Sie verweisen in ihrem Vortrag anlaßlich der 72 Jahresversammlung der Amerikanischen Dermatologischen Gesellschaft in Colorado Springs vielmehr ausdrucklich auch auf die Bedeutung des Ortswechsels fur das emotionale Gleichgewicht Die Patienten gelangen bei einem Klimawechsel in ein ruhigeres psychisches Tempo somit in ein gewisses Gleichmaß das eine allgemeine Ruhigstellung der nervosen Kranken zur Folge hat

Die Bedeutung des Nervensystems und damit indirekt auch psychischer Einflusse erhellt aus einer sehr interessanten Beobachtung von Illig (1954) Die neurodermitischen Hautveranderungen liefen bei einem Kranken stets an den Extremitaten symmetrisch ab Nach einer Poliomyelitis mit Restlahmung des rechten Armes blieb dieser jedoch vollig frei Illig gelangte zu der Schlußfolgerung daß die Änderung des Reaktionsvermogens infolge trophischer Storungen auf einer Änderung des Reaktionsvermogens in Abhangigkeit vom Nervensystem beruhen konne Daruber hinaus sei allerdings auch an eine Zustandsanderung des Hautorgans selbst zu denken

Charakteristisch sind die Hautgefaßreaktionen und der vegetative Tonus *im Bereich des Haut Organs* Untersuchungen von Schuppli aus Zurich sowie Borelli Schatz Kraft Schirren und Spier an unserer Klinik haben ergeben daß durch eine Umstimmung des vegetativen Gefaßtonus — außerlich angezeigt durch Normalisierung der Dermographismusreaktionen — zwar nicht in jedem Falle absolute Erscheinungsfreiheit erreicht werden kann doch erwiesen die Versuche z B mit Hydergin und anderen vegetativ wirksamen Pharmaka daß die erzielte Tonusumstimmung die Normalreaktion des Hautgefaßsystems bewirkt

Milder (Sidney 1955) kommt auf Grund entsprechender Untersuchungen zur folgenden Zusammenfassung seiner Ergebnisse

1 Trager des Neurodermitis Asthma Heufieber Syndroms sind cha

rakterisiert durch konstitutionnelle abnormale Reaktionen bei großer Variabilität der auslosenden Reize

2 Die abnormale Reaktivitat steht in Zusammenhang mit ektodermal kongenitalen Besonderheiten Endokrine Faktoren spielen eine Rolle sowie erhebliche Veranderungen im vascularen Reaktionsbereich und deren Folgen

3 Emotionale Reize sind von großter Bedeutung Ganz bestimmte psychische Einflusse sind oft nachweisbar

4 Umgebungswechsel Klimatherapie, psychologische Behandlung und Elimination aller nachgewiesenen Noxen sind notwendig Die Hormontherapie *kann in Zukunft in vieler Hinsicht bedeutsam sein*

5 Hospitalisation ist nur bei schwereren Fallen angezeigt Die Zusammenarbeit zwischen Dermatologen und Psychiatern (gemeint sind Psychotherapeuten) darf nicht vergessen werden

Den Einfluß von Allergenen — jedenfalls mit unseren Methoden bisher *faßbaren Alllegenen — auf die Manifestation und das Rezidivieren* der konstitutionellen Neurodermitis halten wir auf Grund der neueren Untersuchungen fur unbedeutend bzw bedeutungslos Soweit allergische Reaktionen nachweisbar waren konnten Miescher und Schnyder bspw beobachten daß sie nur in Zusammenhang mit gleichzeitig vorhandenem Asthma bronchiale bzw *mit Rhinitis allergica* (Heufieber) gebracht werden konnten Neurodermitis Kranke die nicht an Asthma bronchiale oder Rhinitis litten reagierten nicht auf Allergene Aus diesem Grunde konnen wir uns d neuerdings (1957) von Diamond geäußerten Vermutung von der Bedeutung der Inhalationsallergene (Hausstaub, Pollen Schafwolle u a) fur die Auslosung neurodermitischer Schube nicht mehr anschließen

Auffallig war uns nun bei unserer Beschaftigung mit dem Neurodermitisproblem daß die akuten Schube des Leidens bzw seine plotzliche Besserung — abgesehen vom Reagieren auf psychische Einflusse — sehr haufig eine *Abhangigkeit von Klima Jahreszeit* und Witterung sowie vom *Klimawechsel* zu zeigen scheinen Wir sind bereits in der Turkei diesen Fragen nachgegangen und haben im Verlaufe der letzten 8 Jahre in Hamburg und Mun

Schnyder in

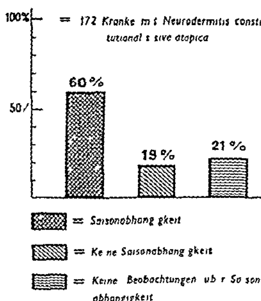
Miescher und Schnyder (Zurich) registrierten das ... aison abhangigkeit nur in 9 5 bis 14 % ihrer Falle Borelli und Eichhoff (Munchen) erhoben die in Tabelle I wiedergegebenen Zahlen

Abgesehen von einer Beeinflussung durch die Jahreszeiten wurde auch ein Variieren der Hautreaktionen entsprechend der Witterung z B Fohn Wetterumschlag usw angegeben

Besonders wesentlich erschien uns jedoch daß Patienten mit wirklich ausgepragter und schwerer praktisch unbeeinflußbarer *Neurodermitis constitutionalis sive atopica* sehr haufig uber *schlagartige Besserungen nach Orts und Klimawechsel* berichteten die auch nach Ruckkehr in das heimische Klima mitunter entgegen dem sonstigen Verlauf des Leidens lange ... jahre

der

gra
sich



Tab I Von 172 Neuroderm stis Kranken gaben nicht wen ger als 103 = 60 % eine Saison (= Jahreszeiten) abhäng gkeit an Nur 33 = 19 % verne nten eine Saisonabhangigkeit 36 = 21 % konnten keine Angaben uber eine Sa sonabhängigkeit machen

NAME DER HOCHGEBIRGS STATION	HOHE UBER DEM MEERES SPIEGEL	AUTOREN	ZAHL DER FALLE	DAUER DES AUFENTHALTES	PROZENT D FALLE MIT DAUER HEILUNG*	MIT BESSE RUNG
Davos	1574	Turban und Spengler	1 3	—	44	27
St Moritz	1769	v Planta	21	über 1 Jahr	40	25
Davos	1574	Burckhardt	89	6 Monate	30	40
Davos	1574	Wolfer	—	3 Monate + m d D nsi b l s erung	70	25
Celerina	1724	Campbell	110	3 7 Monat	56	36
St Mor tz	1 69		—	1 2 Jahre	65	—
Ulud g (Bithy nischer Olymp)	1823	Marchionin	12	3 Monate	—	86

* Nachbeobachtung 5—10 J hr

Tab II E gebniss von Kuren im Hochg bi ge b i Asthmat kern und Kranken mit Neu odermit s d sseminata

am Beispiel verschiedenster Krankheiten wie der Lepra, Orientbeule, Akrodermatitis atrophicans Herxheimer. Was die geographische Verbreitung anbetrifft, so hatte Marchionini die *Neurodermitis constitutionalis sive atopica* in Anatolien unverhältnismäßig viel seltener beobachtet als in Deutschland. Auch die Erscheinungen im frühen Kindesalter waren dort nur selten anzutreffen (Eckstein, Marchionini). Entsprechende Befunde wurden von P. S. Meyer (Haifa) und Kochs (Iraq) erhoben bzw. bestätigt.

Diese Erfahrung machten sich — meist nur in kleinerem Umfange — einige Ärzte zunutze, ohne zunächst allgemeingültige Folgerungen abzuleiten. Marchionini erzielte ausgezeichnete Erfolge bei seinen aus Istanbul stammenden Neurodermitis-Patienten, sobald er sie für einige Monate auf den bithynischen Olymp (Uludag) schickte, wo sie sich in einer Höhe von 1800 m über dem Meeresspiegel aufhalten konnten. Entsprechende Erfahrungen bei Neurodermitikern bzw. Asthmatikern sahen Eidinoff, Pautrier, Turban und Spengler, Burckhardt, Wolfer, Campbell und andere. In *Tabelle II* und III werden die Ergebnisse von Kuren im Hochgebirge be[illegible]
Asthmatikern und Kranken mit [illegible]
wiedergegeben. Zu den Münche[illegible]
Kranke herangezogen, von denen [illegible]
gen beibrachten*).

Unsere eigenen Ergebnisse aus Ankara, Hamburg und München haben wir in Tabelle III zusammengefaßt.

UNIV. KLINIK	GESAMTZAHL DER FÄLLE	EINFLUß DES GEBIRGSKLIMAS			EINFLUß DES SEEKLIMAS			SONSTIGE KLIMAÄNDERUN[illegible]		
		Zahl der Fälle	Besserung	unbeeinflußt	Zahl der Fälle	Besserung	unbeeinflußt	Zahl der Fälle	[illegible]	unbe[illegible]
Ankara	21	16	14	2	0	0	0	5	4	1
Hamburg	54	15	14	1	11	6	5	28	21	7
Muncken	87	58	49	9	12	10	2	17	15	2
In gesamt	162	89	77	12	23	16	7	50	40	10
Unter den in der Spalte München aufgeführten Personen mit Erfahrungen in Gebirgs- oder Seeklima hatten zugleich sonstige Klimaerfeharung								11	5	6
Insgesamt								61	45	16

Tab. III. Einfluß des Klimawechsels bei Fällen von Neurodermitis constitutionalis sive atopica (nach MARCHIONINI, BORELLI und EICHHOFF)

(*) Weitere Untersuchungen laufen.

Grabowski berichtete 1956 uber die Beeinflussung kindlicher Neurodermitis durch das Nordseeklima Die Kinder befanden sich in der Kinderheilstatte und — Klinik des Seehospizes Kaiserin Friedrich auf Norderney Die Zahl der dort behandelten Kinder ist so groß daß sie berechtigte Ruckschlusse erlaubt Der Verfasser ubersieht die Befunde bei 322 Kindern mit konstitutioneller Neurodermitis die sich in den Jahren 1953 54 im Seehospiz befanden Bei ca 15 % machte sich keine Beeinflussung des Leidens durch die Klimatherapie bemerkbar Die ubrigen zeigten selbst wenn die Neurodermitis schon jahrelang bestanden hatte eine auffallige Besserung

Schwarze Meer konnte Linser eine Reihe von Kranken reisen lassen Fuchs (Karl Marx Stadt) hat das Sanatorium Sachsenbaude (ca 1 150 m) eingerichtet

Die Ursache der Wirksamkeit eines Wechsels in extreme Klimata — wie in das Hochgebirge uber 1 500 m — laßt sich noch nicht eindeutig erklaren Die Allergieforschung — wie bereits erwahnt — hat bislang keinen beweisenden Anhalt dafur erbringen konnen daß bei reiner *Neurodermitis constitutionalis sive atopica* ohne Kombination mit Asthma oder Rhinitis allergica Allergene vorliegen Ob bisher nicht erfaßbare Klima und Ortsallergene und deren Elimination durch den großen Klimawechsel eine Rolle spielen ist wissenschaftlich nicht exakt nachweisbar gewesen

Sehr wesentlich durfte die Bedeutung der extremen Umstimmung sein Berucksichtigt man daß Zimmermann bei der Analyse der Harn Steroide unter Einwirkung eines bloßen Wetterfrontendurchganges unter Umstanden eine 50 % ige Erhohung der Nebennierenrinden und Sexualhormonausscheidung (C 17 Ketosteroide) (das bedeutet eine plotzliche Vermehrung um die Halfte) registrierte so durfen wir — bei Anwendung eines radikalen Klimawechsels — auf analoge Bewegungen im Funktionsbereich des vegetativen Nervensystems mit einiger Berechtigung rechnen — Bedenken wir welche Erfolge z B auch durch die Umstimmung im Hor

Die Bedeutung des Einflusses der Psyche muß naturlich auch bei einer Verschickung ins Hochgebirge beachtet werden Fur ein ausgeglichenes gunstiges psychisches Milieu am Ort der Verschickung ist deshalb besondere Sorge zu tragen — Rein klimatisch ist es nach unseren Erfahrungen auch wesentlich daß der Kurort eine moglichst freundliche und gleichmaßige

Witterung aufweist Gegenden mit häufigem Klimawechsel starken Föhnschüben usw dürften nicht sehr geeignet sein

In der Bundesrepublik stehen in Höhenlagen über 1 500 m nur Bergkuppen zur Verfügung Allem Anschein nach kann man bessere therapeutische Wirkungen erzielen wenn der 1 500 m hoch gelegene Kurort sich in einem von noch höheren Gebirgszügen umrahmten Gebirgstal befindet Es gibt Plätze die diesen Anforderungen entsprechen ein hohes Maß von Sonneneinstrahlung aufweisen föhnarm sind und infolge windgeschützter Lage und Talöffnung nach Süden ein ausgesprochen gleichmäßig mildes Klima aufweisen Derartige Plätze finden wir nur außerhalb der deutschen Alpen vor allem in der Schweiz

Die Verschickung in Höhengebiete *über* 1 500 *m* oder an die See in entsprechenden Fällen scheint uns eine sehr bedeutsame therapeutische Möglichkeit bei dem so schwer ärztlich zu beeinflussenden Leiden der *Neurodermitis constitutionalis sive atopica* darzustellen Für besonders wichtig halten wir es auch daß man nicht nur bei therapieresistenten Patienten eine momentane und vielfach lang anhaltende Besserung nach genügend langem Aufenthalt am Höhenklimakurort erzielen kann sondern daß man darüber hinaus auch die Möglichkeit besitzt bei Kranken mit bekannter Saisonabhängigkeit das Auftreten eines neuen Schubes zu verhindern indem man den betreffenden Kranken rechtzeitig verschickt

Die *Dauer der Klimakur* muß möglichst lang bemessen sein Sie dürfte nie unter 6 Wochen liegen Dieser Zeitraum erscheint uns noch fast zu kurz Wir sehen unsere Aufgabe darin geeignete Orte für die Klimatherapie der Neurodermitis constitutionalis ausfindig zu machen und dort die notwendigen ärztlichen und pflegerischen Bedingungen zu schaffen Abgesehen von therapeutischen Erfolgen versprechen wir uns auch neue Ergebnisse für die Erforschung der ursächlichen Bedingungen dieser günstigen Erfolge der Klimabehandlung

ZUSAMMENFASSUNG

Nur wenige Krankheitsbilder weisen zo zahlreiche charakteristische Besonderheiten auf wie die Neurodermitis constitutionalis Im Körperbau fällt das Überwiegen der Leptosomen bzw Leptosom athletischen auf Anthropometrisch wurde nachgewiesen daß rund 61 % überwiegend leptosom 15 5 % athletisch (normaler europäischer Bevölkerungsdurchschnitt zusammen nur 40 50 %) waren — Zugleich ist eine psychische Übereinstimmung der Träger dieser Krankheit feststellbar (Borelli = Spannungscharakter)

Charakteristisch sind die Hautgefäßreaktionen und der vegetative Tonus (im Bereich des Haut Organs jedenfalls) Untersuchungen von Schuppli sowie Borelli Schatz und Kraft haben ergeben daß durch eine Umstimmung des vegetativen Gefäßtonus (äußerlich angezeigt durch Normalisierung der Dermographismusreaktionen) zwar nicht in jedem Fall absolute Erscheinungsfreiheit erreicht werden kann Doch erwiesen die Versuche z B mit Hydergin und anderen vegetativ wirksamen Pharmaka, daß d e

erzielte Tonusumstimmung die Normalreaktion des Hautgefäßsystems bewirkt

Berücksichtigt man daß Zimmermann bei der Analyse der Harnsteroide unter der Einwirkung eines bloßen Wetterfrontendurchganges u U eine 50 $^0/_0$ ige Erhohung das bedeutet eine plotzliche Vermehrung der Nebennierenrinden und Sexualhormonausscheidung (C 17 Ketosteroide) um die Hälfte registrierte so durfen wir — *bei Anwendung eines radikalen Klimawechsels* — auf analoge Bewegungen im Funktionsbereich des vegetativen Nervensystems mit einiger Berechtigung schließen Die Ausschaltung von eventuell existierenden Klimaallergenen und weiteren Faktoren darf man daruber hinaus bei derartigem Klimawechsel vermuten

Nach unseren Erfahrungen bewirkt bei dem konstitutionell relativ gleichartigen Personenkreis der Kranken mit Neurodermitis disseminata eine *Hohenkur in uber* 1 500 *m Hohe* eine allgemeine Umstimmung und vielfach bei genugend langer Ausdehnung eine langere ruckfallsfreie Zeit als bei Anwendung anderer therapeutischer Maßnahmen beobachtbar ist Diese Umstimmung durfte dabei zu einer veranderten Reaktionsweise insbesondere des vegetativen Nervensystems fuhren und ebenfalls wesentlich das psychophysische Zusammenspiel im Gesamtorganismus beeinflussen Wenn auch die konstitutionelle Basis der Neurodermitis disseminata unverandert bleibt so gelingt es doch wenigstens in diesen Fallen mit Hilfe der [illegible]

RÉSUMÉ

Peu de maladies présentent un tableau de particul rites caractéristiques aussi varié que la *né rodermite disséminee*

On remarque en ce qui concerne leur constitution corporelle chez les malades porteurs de cette maladie une predominance marquee de leptosomes et de leptosomes athletiques On rencontre chez ces malades dans leurs caracteres anthropometriques 61 p 100 de leptosomes et 15 5 p 100 de leptosomes athletiques (la moyenne normale etant pour la population de l Europe de 40 50 p 100) On constate egalement dans ce groupe de malades une analogie de structure psychique (Borelli cara teres sous tension)

Les réactions vasculaires cutanees et celles du tonus neuro vegetatif (au niveau des organes cutanés) sont caractéristiques Les experiences de Schuppli et de Borelli Schatz et Kraft ont montre que l on peut (mais pas dans tous les cas) obtenir une disparition totale des symptomes par une modification du tonus vasculaire cutané Ce changement se traduit par une normalisation du dermographisme Il a cependant eté démontre par des expériences faites avec l hydergine et d autres médicaments neuro végetatifs que les modifications du tonus ainsi obtenues influencent les réactions normales du systeme vasculaire cutane

Si l'on tient compte du fait observé par Zimmermann qu'à la suite d'une simple et courte période de temps orageux une augmentation urinaire de 50 p 100 des stéroïdes se produit (ce qui correspond à une augmentation de moitié de l'élimination normale des hormones surrénaliennes et sexuelles — 17 cétostéroïdes —) on peut admettre qu'un *traitement par changement radical de climat* puisse provoquer des fluctuations analogues dans le domaine fonctionnel du système neuro végétatif On peut supposer que lors de semblables changements de climat l'activité des allergènes climatiques et aussi d'autres facteurs cesse de s'exercer

Notre expérience personnelle nous a appris que pour l'ensemble des sujets atteints de névrodermite disséminée et constitutionnellement assez semblables *une cure d'altitude de plus de* 1 500 *mètres* amenait en général un renversement du cours de la maladie et que dans les cas de cures assez prolongées il était possible d'obtenir des périodes sans rechutes plus longues que celles que peuvent procurer d'autres méthodes de traitement

Il est permis de penser que ce renversement de tendance de la maladie amène une modification dans le type même des réactions et plus particulièrement pour celles du système neuro végétatif on peut penser ainsi qu'il exerce une action sur l'ensemble psychophysique de l'organisme

Sans pour cela pouvoir changer la base constitutionnelle de la névrodermite on peut cependant parvenir à rompre le « cercle vicieux » en utilisant en dernier ressort la cure d'altitude

L'observation méthodique des malades dans les stations d'altitude au point de vue des modifications fonctionnelles apportera peut être des éléments nouveaux dans le domaine des recherches sur la névrodermite disséminée

SUMMARY

Only few diseases display such typical and various peculiarities as disseminated neurodermatitis

From the view point of their bodily constitution one notes among patients suffering from the di ... predominance of leptosomes and athletic leptosom ... p 100 of leptosomes and 15 5 p 100 c ... normal *for the population of Europe* ... psychical concordance in the patients suffering from this disease (Borrelli — Psychical strain)

Skin vascular reactions are typical The evidence brought by Schäppli and Borrelli, by Schatz and Kraft suggests the possibility of a total disappearance of the symptoms but not in all cases by changes of the vascular vegetative tonus of the skin This change is reflected by the return to normal of the dermographismus

Nevertheless experiments carried out with Hydergene and other pharmacological compounds active on the vegetative tonus have brought proof that the changes obtained in the tonus have their influence on the normal reaction of the skin's vascular system

Considering the findings of Zimmermann who after a simple and short

spell of stormy weather has noted a 50 p 100 increase of the urine s steroids (which means a 50 p 100 increase of the elimination of adrenal cortex and sexual hormones — C17 Ketosteroids) one may well admit that a treatment consisting in a *radical change of climate* is likely to bring about similar movements in the functional activity of the neuro vegetative system One may also assume that as such changes of climate occur the climatic allergens and besides other factors lose their aggressive potentialities

Personal experience has taught us that for the type of patients suffering from disseminated neurodermatitis and showing an almost similar constitution *a cure at an altitude above 1500 meters* generally brings about a drastic change in the course of the disease and that in the case of long cures one could gain thus longerlasting relapse free periods than what can be achieved with any other treatment

One may assume that the change of course of the disease modifies the type of reactions particularly in the neuro vegetative system and that its influence is also exerted on the whole psychophysical condition of the organism

Although the constitutional basis of the neuro dermatitis remains unchanged we can with the altitude treatment in the last instance succeed in breaking through the vicious circle

The methodical observation of patients in high altitude resorts in regard to their functional changes will perhaps bring new facts in the field of researches on disseminated neurodermatitis

RESUMEN

En pocas enfermedades se observa un conjunto de particularidades características tan variadas como en las neurodermitis

En lo que respecta a su constitucion corporal se observa en los enfermos una marcada predominancia de leptosomas y leptosomas atléticos (61 p 100 y 15 5 p 100) respectivamente siendo la media normal en Europa de 40 50 p 100 Se constata igualmente en estos enfermos una estructura psiquica analoga (Borelli)

Las reacciones vasculares cutaneas y las del tono neurovegetativo (al nivel de los órganos cutáneos) son características Las experiencias de Schuppli y Borelli Schatz y Kraft han demostrado que es posible (aunque no en todos los casos) lograr una desaparición total de los síntomas por una modificación del tono vascular cutáneo Este cambio se traduce en una normalización del dermografismo Ha sido demostrado sin embargo en experiencias realizadas con hydergina y otros medicamentos neuro vegetativos que las modificaciones del tono asi obtenidas influencian las reacciones normales del sistema vascular cutaneo

Si se tiene en cuenta la observación de Zimermann que luego de un simple y corto período de tiempo tormentoso se produce un aumento de 50 p 100 en los esteroides urinarios puede admitirse que un *tratamiento de cambio radical de clima* llegue a provocar fluctuaciones analogas en el dominio funcional del sistema neuro vegetativo Puede suponerse que al cambiar de clima dejan de actuar los alergenos climaticos y otros factores

Nuestra experiencia nos indica que en los pacientes de neurodermitis diseminada *una cura de altitud de mas de 1500 metros* produce en general una evolución favorable de la enfermedad y que cuando la cura se prolonga es posible obtener largos periodos sin recidivas mayores que los obtenidos con otros tratamientos Puede suponerse que se produce una modificació en el tipo mismo de reacciones del sistema neuro vegetativo y del conjunto psicofisico del organismo Sin que ello llegue a cambiar la base constitucional de la neurodermitis puede no obstante romperse el «circulo vicioso» mediante la cura de altitud

La observacion metódica de los pacientes en las estaciones de altura desde el punto de vista de las modificaciones funcionales aportará sin duda nuevos elementos para las investigaciones sobre la neurodermitis diseminada

ON THE IMMUNITY IN ATOPIC DERMATITIS

by

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Most dermatologists and allergists take it for granted that atopic dermatitis is an allergic disease Only a few years ago it together with other forms of the true eczema was considered to be an autotoxic rather than an allergic dermatosis

Indeed the case histories of many patients suffering from atopic dermatitis leave little doubt as to the allergic nature of their disease But aside from these text book cases we encounter quite a number of others in which the allergic origin is not apparent particularly when the causative agent remains unknown even after intensive search

In spite of all the weight of indications it is not correct to make the generalization that each case of atopic dermatitis is an allergic disease We find the same situation in other forms of allergies it is known that practically all typical allergic symptoms such as dermatitis urticarial wheals asthma and shock may occur as purely pharmacologic toxic and non allergic reactions produced either by certain primary toxic substances or by the so called histamine releasers and without any association with specific antibodies It is quite probable that certain symptoms of atopic dermatitis occur likewise as purely toxic reactions simulating an allergic origin and atopic dermatitis may also be caused by the non allergic release of certain endogenous toxic substances Thus certain substances contained in foods or fibers including simple chemicals can release this unidentified allergotoxin in the same way as for instance 48/80 releases histamine It is indeed reasonably certain that the typical eruption of atopic dermatitis is not caused by histamine but by some other and as yet unidentified allergotoxin In general the number of clinical cases in which a histamine releaser simulates a true allergy is not large compared to true allergies and I believe this is also the case with these examples of non allergic atopic dermatitis

Our whole knowledge of the origin and pathology of atopic dermatitis derives from clinical observations including experimental exploration with various diagnostic skin tests Although such tests are often positive in

atopic dermatitis they are often nonspecific and thus for diagnostic purposes less reliable than positive reactions in other allergic diseases Besides skin and passive transfer tests we have virtually no experimental or even semi experimental data on atopic dermatitis and an analysis of the immunological status of atopic dermatitis must therefore rely on secondary evidence such as the analysis of certain symptoms that are characteristic of atopic dermatitis

Such symptoms are the paroxysmal pruritus the skin eruptions alternating with asthma the fact that the skin of patients with atopic dermatitis shows a surprisingly low degree of unspecific hypersensitivity to non specific irritants and the predilection of the disease for certain skin areas

Pruritus is considered by some to be a regular companion of atopic dermatitis but not as the cause of the disease in much the same manner that pruritus regularly accompanies urticaria and anaphylactic shock pruritus of itself does not produce any of these manifestations Other allergists and dermatologists consider pruritus as the real primary caus of atopic dermatitis It is difficult to decide who is closer to the truth since the physio pathology of pruritus is not clearly understood But we know that pruritus may be induced by both immunological and non immunological processes One regular cause of pruritus is the release of histamine or a histamine like substance If the source of histamine is an antigen antibody reaction then the pruritus is an immunological manifestation But when a histamine releaser initiates the chain of reactions the ensuing pruritus is a non allergic purely toxic reaction The shock like paroxysmal attacks of pruritus so characteristic of atopic dermatitis are not necessarily proof of the latter s allergic nature we know that histamine is released explosively by a non antigenic releaser such as 48/80 in just the way it is momentarily released by an antigen antibody reaction

Consequently all those who regard pruritus as the primary cause distinguish between allergic and non allergic varieties of atopic dermatitis depending upon whether the pruritus is a consequence of an antigen antibody reaction or of a non immunological process or agent such as an external irritant sweat retention psychological disturbances, etc

Sometimes the *allergen* responsible for atopic dermatitis is well known to the patient But if he does not know the origin of his disease the allergist can rarely detect the causative agent in spite of suspected positive skin tests This does not prove as many investigators imply that there is no allergen It only proves in most instances that enough tests were not made

Sensitizing agents known to produce atopic dermatitis are components of food silk wool animal hair dander pollen microorganisms etc It is the general opinion that the active allergens in these natural products or microorganisms are proteins—but this is by no means certain Among the proteinic allergens fibrous and globular proteins are apparently equally antigenic Moreover these complete antigens numerous well defined chemicals of low molecular weight as for instance paraphenylenediamine formaldehyde persulfates certain alkaloids, etc are *frequent* causes of atopic dermatitis

This is a widely diversified collection of allergens with the most varied chemical and physical properties In spite of this diversity in the chemical and physical nature of the allergens involved I believe that certain common

properties of these allergens in addition to certain tendencies of the patient s constitution toward atopic reactivity are necessary to produce atopic dermatitis

The nature of the *antibody* directly responsible for atopic dermatitis is quite unknown Positive immediate skin reactions after skin tests with suspected material or positive passive transfer indicate the presence of humoral antibodies in many pateints But it is by no means established that the antibodies revealed by these skin tests are the actual antibodies involved in and responsible for the patient s dermatosis In numerous instances these humoral antibodies although part of the patient s specific allergy are evidently not responsible for the characteristic skin manifestations of atopic dermatitis rather they are antibodies connected with a concomitant sensitization affecting other reactive sites than those of the dermatitis They may be parts of the alternating asthma and urticarial vascular reaction which is only one part of the histological picture of atopic dermatitis As we shall discuss presently it may be po sible that positive skin tests of the whealing type are so called non specific positive also in atopic dermatitis Such unspecific reactivities are regular companions of acute states of hayfever So far as positive patch tests are concerned we encounter quite peculiar conditions in atopic dermatitis Whereas in contact dermatitis positive patch test reactions are often expressions of a generalized unspecific non allergic hyper reactivity of the skin but not indications of the presence of specific sessile antibodies unspecific skin reactivity is a rather rare occurence in atopic dermatitis

In spite of this very scant knowledge it is interesting to speculate as to what *type of antibody* could be connected with atopic dermatitis As mentioned above we may gain information from the carriers to which the antigens become attached

It is known that haptenic antigens require a carrier usually a protein in order to become full antigens Evidently the chemical nature of this carrier can vary considerably from case to case depending upon how the body is exposed to the hapten and probably also upon the nature of the hapten involved In another symposium of this Congress I discussed the reasons for believing that the physical properties of the carrier moiety determine the type of antibody and that atopic dermatitis is connected with a special antibody

According to clinical data and the histological picture atopic dermatitis should be considered not merely a combination of the evanescent and contact type but a special type of sensitization in which the ground substance of the skin is the specific site of sensitization This is indicated by the hyper trophy of the collagen bundles of the connective tissue which is often considerable in atopic dermatitis and the characteristic changes in the histo chemical behavior of the mucoproteins of the connective tissue particularly a depolymerization of the ground substance The simultaneous hyper trophy of the collagen and the depolymerization of the mucopolysaccharides of the ground substance in atopic dermatitis can be explained by the fact that mucopolysaccharides coat the collagen fibres

The particular participation of collagen and ground substance suggests the presence in atopic dermatitis of an antibody in the formation of which antigens associated with the polysaccharides of the ground substance play

an important part Evidently such an antibody would differ from the humoral and sessile antibodies as well

We know little of the immunological aspects of the *combination* and in particular the highly characteristic *alternation of atopic dermatitis and asthma* in the same patient In many instances both manifestations are produced by the same antigen many patients in the fur dyeing industry for instance know from experience that their asthma is caused by the vapors of oxidized p phenylenediamine and their alternating atopic dermatitis by dust of the dye particles Furthermore many of these patients perpetuate their skin eruptions by continuous external use of their known allergen in order to postpone or prevent the appearance of the alternating asthma which is far more disabling than the dermatosis A very similar alternation or at least a reciprocal relationship between two different types of sensitizations involving different antibodies is known in experimental sensitizations of guinea pigs with azo antigens in these animals the same chemical first produces an anaphylactic type of hypersensitiveness which is then superseded by the delayed type

Another well established fact peculiar to atopic dermatitis and which distinguishes this allergy sharply from contact dermatitis has not yet received the attention it deserves namely the *low incidence of unspecific polyvalent hypersensitivity* of patients with atopic dermatitis to *primary skin irritants* which we have already mentioned The skin of most patients suffering from acute or subacute contact dermatitis or eczema is highly hyperreactive to numerous mostly heterogenous substances unconnected with the specific antigen in these cases the great number of indiscriminately positive patch tests simulate the true antigen But the skin of patients presenting manifestations of atopic dermatitis has a normal or even an abnormally low unspecific reactivity toward these unconnected substances We do not know the reasons for this very surprising observation which was first made by J Jadassohn in particular we do not know whether it has any relations to the specific immunological process An exploration of this phenomenon should certainly reveal interesting results

Since similar polyvalent unspecific hypersensitivities of the immediate type exist in the acute states of hay fever and urticaria we may learn for instance whether the low unspecific skin sensitiveness in atopic dermatitis concerns not only the delayed type of reactivity but also the evanescent type Unspecific reactivity of this evanescent type is sharply increased during the acute state of hayfever we know much less about any such increase in atopic dermatitis

I mention only briefly the *typical localization* of atopic dermatitis in the flexural parts of the body, without being able to propose any explanation for this unusual predilection

Contact dermatitis and urticaria asthma and shock have been reproduced in experimental animals many times but we have not yet succeeded in producing atopic dermatitis Of all recognized allergic processes atopic dermatitis has been explored the least Only when we are able to study the various phases and conditions of this disease in animals can we find the true answers to the questions which today we have tried to solve with indirect proofs analogies and, to a large extent speculation

SUMMARY

The author discusses the following clinical pathological and experimental observations which are in agreement with the concept of the allergic origin of atopic dermatitis The nature of the paroxysmal pruritus which is in most cases the immediate consequence of an antigen antibody reaction the nature of the responsible allergens the type of exposure leading to different types of sensitizations the nature of the antibody concerned which is possibly different from both the humoral antibodies of urticaria or serum disease and the sessile antibodies of the delayed type of allergy Also discussed are the combination and alternation of atopic dermatitis and asthma and the surprisingly low incidence of unspecific polyvalent hypersensitivity in atopic dermatitis

RÉSUMÉ

L auteur discute des observations cliniques pathologique et experimentales en rapport avec la conception de l origine allergique de l eczema diathesique Ce sont

— la nature du prurit paroxystique qui est dans la plupart des cas la suite immediate de la reaction antigene anticorps

— la nature de antigenes responsables

— les differents genres d exposition provoquant les different types de sensibilisations

— la nature de l anticorps implique qui est peut etre different des deux types d anticorps les anticorps humoraux de l urticaire et de la maladie du serum et les anticorps sessiles des types d allergie a reactions differees

Il est également discute de la combinaison et de l alternance de l eczema diathesique et de l asthme et aussi de l influence étonnamment reduite de l hypersensibilite non specifique polyvalente sur l eczéma diathesique

ZUSAMMENFASSUNG

Der Autor diskutiert klinische pathologische und experimentelle Beobachtungen in Zusammenhang mit der Vorstellung einer allergischen Ursache des Diathesie Ekzems Sie sind

— die Natur des anfallsweisen Juckens das in den meisten Fallen die unmittelbare Folge der Antigen Antikorper Reaktion ist

— die Natur des zustandigen Antigens

— die verschiederen Expositionsarten die verschiedenen Sensibilisierungs typen bedingen

— die Natur des beteiligten Antikorpers der eventuell von 2 anderen Antikorpern zu unterscheiden ist die humoralen Antikorper bei der Urticaria und der Serumkrankheit und die gebundenen Antikorper verschiedener Allergieformen

Weiterhin wird die Verbindung und der Wechsel von Diathesie Ekzem und Asthma diskutiert eben o der erstaunlich geringe Einfluss einer nicht spezifischen polyvalenten Ueberempfindlichkeit auf das Diathesie Ekzem

RESUMEN

El autor discute las observaciones clinicas patológicas y experimentales que están de acuerdo con el concepto de que la dermatitis atopica es un trastorno alergico Se refiere a la naturaleza del prurito paroxismal que en la mayoría de los casos es la consecuencia inmediata de la reacción antígeno-anticuerpo a la naturaleza de los alergenos responsables al tipo de exposición que conduce a diferentes tipos de sensibilización a la naturaleza de los anticuerpos posiblemente distintos de los anticuerpos humorales de la urticaria y la enfermedad del suero y de los anticuerpos sesiles de los tipos tardios de alergias Asimismo se refiere a la simultaneidad y alternancia de la dermatitis atópica y el asma y a la sorprendente pequeña incidencia de hipersensibilidad polivalente inespecífica en la dermatitis atopica

UNE QUESTION ÉPINEUSE DE NOMENCLATURE LE SYNDROME ECZÉMA PRURIGO ATOPIQUE (BESNIER SULZBERGER) DIT DERMATITE ATOPIQUE

par

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Rien ne peut mieux souligner les divergences auxquelles donne lieu ce point de nomenclature medicale que l annonce meme du theme dans les bulletins de ce Congres On nous appelle en effet a l etude de « l eczema diathesique » en langue française mais aussi de l atopic dermatitis en anglais enfin « endogenes ekzem » en allemand On dirait deja une sorte de defi à l adresse du rapporteur Ajoutons encore a cette liste les expressions de « neurodermatitis » et de « prurigo Besnier » et nous aurons groupe les denominations les plus en usage dans ces derniers temp Et il y en a pas mal d autres

Nous ne ferons aucune difficulte pour admettre que chacune d elles contient une part de verite et que tout le monde a certainement un peu raison Cependant toute question de nomenclature se rattachant a un acte de l intelligence il n y a d autre moyen d en sortir que de discuter tout le sujet sous cet angle Qu il me soit permis de rappeler le conseil de Rille lorsqu il recommande d avoir toujours « hinter jedem unserer dermatologischen Termine eine morphologische Wirklichkeit hinter jeden Worte ein Begriff »

Il n est donc pas surprenant que l etude de cette question ait ete amorcee par le coté clinico morphologique et qu ainsi F Besnier (1) ait pu identifier cet important tableau clinique en 1892

Deja à cette epoque les lesions caracteristiques etaient decrites comme etant « eczémato lichéniennes » et subordonnées à une donnée basique fondamentale le *prurit* (selon Besnier premier symptome et symptome premier ») Et le nom propose etait celui de prurigo diathesique » a type eczemato lichenien

Il est curieux et c est un fait bien certain que la description inaugurale de Besnier ne trouvât pas accès auprès des dermatologues français et que son

nouveau type morbide ne fut aussitot reconnu en France Les descriptions admises dans les ouvrages du temps etaient pour le moins assez diffuses ou nettement insuffisantes Écrivant dans le grand traite en langue français — la *Pratique Dermatologique* — L Jacquet (2) nous parle d'une façon assez imprecise « des varietes nombreuses des erythemes infantiles des urticaires des pseudo lichens ou l une des formes d eczematisation ou de lichenisation » qui peuvent a son avis composer la physionomie clinique de notre syndrome Pas un mot sur la topographie si caracteristique des lesions ni sur l aspect general non moins typique des malades

Comment s etonner apres cela que des maitres comme L Brocq et J Darier eux memes ne se montrent pas autrement informes sur les exactes caracteristiques et proportions du syndrome isole par Besnier

Écrivant en 1908 Darier (3) avoue les incertitudes de sa position il ecrit « ni la description princeps du createur de ce type qui en faisait une variante du prurigo de Hebra ni celle de Jacquet et d autres ne sont suffisantes pour l individualiser nettement vis a vis du *prurigo simplex* » Et plus bas en décrivant le prurigo de Hebra Darier nous parle de « ce qu on a appele le type français » de cette forme

Écrivant en 1896 plus tard en 1919 L Brocq (4) decrit et etudie un cas typique avec ce commentaire « c est donc un prurigo avec eczém i sation et lichenification c est a dire cette variete de prurigo a laquelle E Besnier a donne le nom de prurigo de Hebra » Un peu plus loin il ajoute « et cependant vous n avez pas sous les yeux le vrai prurigo decrit par Hebra aussi ai je cru devoir donner a cette vari te il y a de longues annees le nom de prurigo dit de Hebra variete française » (a remarquer dans ce meme texte excellemment presente comme toujours chez Bro q deja une anticipation des contributions si interessantes de Marchionini lorsque l auteur français nous parle des bienfaits des cures d altitud « au dessus de 1 400 metres »)

Il faudra arriver a 1913 pour rencontrer les témoignages independants et egalement importants de R Sabouraud (5) et surtout de C Ras h (6) Sabouraud un ancien disciple de Besnier, propose avec Ras h de separer plus nettement que ne l avait fait Besnier lui meme ce type morbide du prurigo de Hebra Rasch étudie trente cas bien observes parmi lesquels cinq compliques d asthme et propose le nom de « prurigo Besnier » Sabouraud lui aussi (« prurigo asthme ») nous donne une parfaite description du tableau chez l enfant et chez l adulte en anticipant deja sur la classique description evolutive de Hill et Sulzberger (voyez cependant plus haut au sujet des cures de montagne et que penser lorsque Sabouraud ecrit chose remarquable cette affection m a paru s ameliorer toujours au bord de la mer »)

C est beaucoup plus tard en 1925 qu un disciple de Rasch H Haxthau sen (7) complète l inventaire des signes cliniques en signalant la curieuse immunite du cuir chevelu (et des cavites axillaires!) au cours du syndrome la complication frequente non seulement par l asthme mais aussi pa l icthyose vulgaire l influence nuisible de la lumiere solaire en meme temps que les tests percutanes perme tent a Haxthausen une critique gene rale des reactions positives obtenues par les auteurs nord americains dans nombres « d eczémas generalises » plutot des faits non diagnostiques de notre eczema prurigo Ces cuti reactions negatives dans les dermatoses

confondues avec le type de Besnier « les nevrodermites les autres formes de prurigo les eczemas chroniques » sont correctement interpretees par Haxthausen comme autant de faits cliniques favorables a la separation de ce type morbide

Vers 1929 1935 se placent les contributions de A Civatte G Rost et A Marchionini sous l angle pediatrique le rapport (et le livre) de E Moro enfin a un point de vue plus général le travail de L W Hill et M B Sulzberger

Ces travaux sont a plusieurs points de vue importants tout a la fois par les precisions qu ils apportent et par la quantité de faits nouveaux signales

L interet majeur de l apport de Civatte (8) ne reside pas seulement dans la description precise de la physionomie génerale du prurigo de Besnier mais tout aussi bien dans la nette differenciation histologique dont la formule « lichenification + lésions vesiculo ulcereuses de l eczématisation + et au premier rang lesions de grattage des teguments inflammés » n a certainement rien de commun avec la lesion dermique profonde du prurigo de Hebra (celui ci caractérise surtout par l infiltrat de polynucleaires neutrophiles formant un nodule central ephemere a leucolyse leucocytoclasie)

Avec Rost et Marchionini (9) on se rend compte du caractere vraiment syndromique de notre type morbide la constitution leptosomique des malades l eosinophilie et la lymphocytose la relative hypoglycemie l hypoacidite gastrique les stigmates anamnestiques (heredite asthme) et — the last not the least — les reponses a des allergene divers Les auteurs proposent de reunir tous ces faits sous le nom de eczéma oide exsudatif » en y comprenant aussi bien les formes infantiles precoces que les formes tardives » de l adolescent et de l adulte

La position alors adoptee par Moro (10) est assez differente Lui aussi refuse toute identite entre le syndrome en question et le vrai prurigo infantile (« strophulus ») il n admet pas davantage un rapport avec l erythrodermie type Leiner qu il rattache a la dermatite seborrhoide (les auteurs allemands ne semblent pas avoir reconnu l existence de vraies érythrodermies dans le cours de l eczema prurigo cf a ce sujet les exactes observations de L W Hill dont nous parlerons tout a l heure) Une fois ces exclusions faites Moro admet a cote du vrai *eczema infantum* c est a dire des formes nettement exsudatives du nourrisson les formes plus ou moins nettement marquees par la lichénification — neurodermitis (« Juckneurose) et que nach Beobachtungen von Czerny Epstein und Neuland im hoeheren Grade psychisch beeinflussbar ist als anderen Ekzemen

C est avec le travail deja classique de L W Hill et M B Sulzberger (11) que l on a pu avoir sous les yeux une description complète du syndrome avec sa phase franchement exsudative papulo vésiculeuse du nourrisson signee du point de vue biologique par les reponses nettes et régulieres aux atopenes alimentaires et assez fréquemment compliquee d une « tendance séborrhéique assez marquee Les premiers ces auteurs decrivent l érythrodermie atopique sur seborrhéique et à ce propos remarquons qu on ne semble pas avoir signalé chez les nourrissons les cas mixtes d eczéma prurigo + seborrhoide (cf cependant chez Finkelstein pro Tachau contra) selon notre expérience personnelle ces combinaisons ne sont pas douteuses nous avons meme pu avoir de rares cas chez l adulte (tout dernierement chez l enfant L W Hill) (12)

En outre Hill et Sulzberger poursuivent leur minutieuse analyse chez l enfant puis chez l adolescent et l adulte ou l affection commence vers la puberte et ils observent l importance croissante des atopenes d ambiance et aussi de certains aliments Discutant la question terminologique ils proposent le terme de « dermatite atopique » (un terme deja employé par Sulzberger en 1932) et admettent que « dermatite a opique chronique » ou « eczema atopique chronique » soient des termes acceptables pour l affection si on ne desire pas l appeler « neurodermatitis »

Jusqu ici nous nous sommes efforces de reproduire a grands traits le [illegible] touchant le syndrome [illegible] , pose deja comme [illegible] dechiffrable au seul point de vue clinico morphologique

Aujourd hui meme alors que la question a pu etre examinée a fond sous les angles les plus divers depuis l appre iation social his orique (Marchionini) jusqu a ses aspects de reaction neuro vegé ative et psychosomatique (M Obermayer), on peut a bon droit s etonner que tant d etudes exactes n aient pas pu liquider la persistante et au fond presque academique question de terminologie

Nous aurons toujours a choisir en médecine entre les designations d [illegible] gine plus ou moins nettement clinico morphologique et celles calquees sur l étio pathogenie La tâche semble tout indiquee de *combiner dans le meme nom* les deux donnees — clinique et pathogénique Cependant meme limitees par ces donnees de base il reste au moins deux solutions possibles à la question terminologique

— ou bien on dira comme le voulut Kreibich *Prurigo Ek em* (en langue latine ce serait plutot eczéma prurigo) en lui accolant l epithete pathogenique *atopique* pour le distinguer des formes voisines non a opiques

— ou bien un peu dans le sens indique jadis par Jadassohn on rese verait le mot eczema exclusivement pour l eczema de contact et toutes les autres formes seraient des « dermatites » (atopique séborrhoide nummulaire)

Ici nous croyons devoir faire mention des idees récemment emises par Pillsbury (1952 1953) (13) car on ne saurait négliger une opinion émanant d une aussi forte personnalite et du groupe qu il represente

Il faut avouer que l idee que tous syndromes « dermatitiques » sont « essentiellement » similaires est plutot surprenante car elle nous mènerait à rattacher de nouveau (dans le vieux sens de Hebra) le *lichen simplex chronicus* aux formes d eczéma ! Ce serait un recul vers 1886 lorsque Vidal liquida le debat avec Hebra en montrant — et après lui Brocq — que des lésions de lichenification circonscrite pouvaient exister et durer *indefiniment seches et non eczematisées* demonstration que nous pourrions aujourd hui compléter en reconnaissant avec Sulzberger qu il n y a rien la qui ressemble à *la vraie* forme eczematoide a opique

Nous ne croyons pas non plus qu on puisse accepter de rattacher aux formes d eczema la *stasis dermatitis* Il convient de rappeler non seulement que l examen general de ces malades est tres dissemblable mais aussi et surtout que l histologie pathologique est *totalement et nettement differente* avec des lesions vasculaires qui lui sont propres (cf les classiques travaux de M Favre — « Angiodermatite » « Dermatite pre érosive » 19 4 1935

aussi bien que notre expérience personnelle — nonobstant le fait certain que l'on puisse avoir de vrais eczémas de contact par substances chimiques ou micro-organismes comme complication de cette forme)

Dans sa présentation d'ailleurs excellente des différentes formes d'eczéma Pillsbury fait une étude poussée (« factorial analysis » Stokes) des facteurs communs à tous types c'est à dire 1° le prurit 2° la rétention sudorale (on pourrait dire sisthidrosis par opposition à dyshidrosis) 3° l'infection secondaire et 4° l'eczéma de contact secondaire C'est très juste et comme toujours remarquablement bien observé Il faudrait toutefois ne pas oublier le fait fondamental que le prurit et la sisthidrose se manifestent bien plus nettement dans notre eczéma prurigo que dans un simple eczéma de contact (la rétention sudorale joue certainement un rôle dans nombre d'eczémas de contact *professionnels* et aussi bien dans tout le groupe séborrhoïde)

Il resterait encore à examiner l'idée suivant laquelle la « dermatite atopique » — de même que le *lichen chronicus circumscriptus* — ne serait pas eczémateuse parce qu'exempte primairement de la spongiose intra épidermique

Nous croyons au contraire que le fait de la spongiose à lymphocytes est certainement un fait général et sur ce point nous avons l'appui précieux de Miescher (14) qui confirmant notre expérience personnelle signale qu'il a rencontré ce type de lésion depuis les eczémas de contact jusqu'aux eczémas nummulaires et jusqu'au plus authentique eczéma prurigo atopique (« endogène »)

En vérité l'étude comparée de « l'eczéma » et des autres grandes formes inflammatoires (surtout celles non infectieuses) montre que l'épiderme lorsqu'il est sollicité (du dedans ou du dehors) répond toujours d'accord avec la norme c'est à dire avec eczématisation ce qui ne veut pas dire que des stimuli se faisant sentir au niveau du corps papillaire ne puissent pas eux aussi provoquer de l'eczéma comme si une action directe s'exerçait sur l'épithélium susjacent en un mot il existe une unité fonctionnelle entre les deux plans Rappelons que Jadassohn discutant ce point a dit « il faudrait penser en une altération de l'épithélium qui se maintient au dessous des limites de la lésion eczémateuse cliniquement manifeste »

La « dermatite » est ainsi tout au plus potentielle et toujours masquée dans la plupart des formes (non compliquées) d'eczéma alors qu'elle apparaît en pleine évidence dans le groupe érythème urticaire (prurigos) érythrodermie et dotée d'un caractère négatif dans l'érythème et dans l'urticaire c'est à dire sans comporter de grosses lésions de l'épithélium tandis que de telles lésions sont au contraire présentes et même précoces mais secondaires dans les érythrodermies (cf nos travaux sur la topographie comparée de l'inflammation cutanée et la systématique des eczémas (15 16)

La notion d'un *parenchyme cutané* (Kromayer 1896) proposant l'unité fonctionnelle épiderme + corps papillaire en transcendant la classique discrimination à base embryologique en faveur du critérium fonctionnel (« Resonanzboden »-Riecke) permet de considérer *toutes* les formes d'eczéma comme des inflammations à composante parenchymateuse dominante *au seuil* des vraies dermatites interstitielles profondes

Sous ce point de vue l'*eczéma prurigo atopique* type Besnier Sulzberger

et sa variante non atopique nummulaire sont précisement des faits posés en jalons a la limite des eczemas et de certaines dermatites interstitielles relativement plus profondes

RÉSUMÉ

Nous aurons toujours a choisir en médecine entre les conceptions plus ou moins clinico morphologiques et celles basees sur l étio pathogénie Il semble tout indiqué de combiner dans le meme nom les deux données clinique et pathogenique Au moins deux solutions restent possibles au point de vue terminologique

— ou bien on dira comme le voulait Kreibich *Prurigo Ekzem* (en langue latine ce serait plutot eczema prurigo) en lui accolant l epithete pathogénique *atopique* pour le distinguer des formes voisines non atopiques

— ou bien un peu dans le sens indiqué jadis par Jadassohn on reserverait le mot eczema exclusivement pour l eczema de contact et tous les autres formes seraient des « dermatites » (atopique séborrhoide nummulaire)

La notion d un *parenchyme cutane* (Kromayer 1896) qui fait etat de l unite fonctionnelle épiderme + corps papillaire en negligeant la classique discrimination a base embryologique en faveur du criterium fonctionnel (« Resonanzboden » Riecke) permet de comprendre *toutes* les formes d eczéma comme des inflammations a composante parenchymateuse dominante *au seuil* des vraies dermatites interstitielles profondes

Sous ce point de vue l *eczéma prurigo atopique* type Besnier Sulzberger et sa variante non atopique nummulaire sont precisement des formes cliniques a la limite des eczemas et de certaines dermatites interstitielles relativement plus profondes

SUMMARY

In medecine we shall always have to make a choice between more or less clinico morphological conceptions and other ones based on etio pathogenesis

It seems advisable to put together in the same name these two basic ideas both clinical and pathogenetic

From the terminological point of view at least two solutions are possible

— Whether should we say (after Kreibish) Prurigo Ekzem what in Latin languages would rather be Eczema Prurigo and we should add the pathogenetic appellation atopic to distinguish it from other similar non atopic forms

— Or we should following to a certain extent Jadasohn s former indications, only use the term eczema for contact eczema and all the other types would be called dermatitis (atopic seborrhoid nummular)

The notion of a *cutaneous parenchyma* (Kromayer 1896) based on the functional unity epidermis + papillary body neglects the classical discrimination based on embryology in favour of the functional criteria of eczema

such as predominating parenchymatic inflammation on *the threshold* of true penetrating interstitial dermatitis

From this point of view *Atopic Eczema Prurigo* from the Besnier Sulzberger type and it s non atopic nummular variety are on the very verge of eczemas and of interstitial dermatitis of a relatively more penetrating species

ZUSAMMENFASSUNG

In der Medizin mussen wir immer zwischen mehr oder weniger klinisch morphologischen oder andererseits atio pathogenen Konzeptionen wahlen

Es scheint ratsam zu sein diese beiden Grundideen die klinische und pathogene im selben Namen zusammenzufassen

Vom terminologischen Standpunkt aus sind wenigstens 2 Moglichkeiten durchfuhrbar

— Entweder sollen wir (nach Kreibisch) Prurigo Ekzem in Latein ware besser Eczema Prurigo sagen und um einen Unterschied zu anderen ahnlichen nicht atopischen Formen treffen zu können den pathologischen Namen atopic zufugen

— Oder sollen wir indem wir bis zu einem gewissen Grade die fruheren Indikationen von Jadassohn befolgen den Terminus Eczema nur fur Kontaktekzeme benutzen und all die anderen Typen Dermatosen nennen (atopisch eborrhoisch nummular)

Der Begriff eines *Kutanparenchyms* (Kromayer 1896) der in der funktionellen Einheit Haut + Papillarkorper begrundet ist vernachlassigt den klassischen embryologisch bedingten Unterschied zu Gunsten der funktionellen Ekzemkriterien so wie vorwiegend parenchymatose Irritationen *an der Schwelle* zu echten penetrierenden interstitiellen Dermatosen

Von diesem Standpunkt aus liegen Atopic Eczema Prurigo vom Besnier Sulzberger Typ und dessen nicht atopische nummulare Varietaten an der Grenze von Ekzemen und interstitiellen Dermatosen einer relativ mehr penetrierenden Art

RESUMEN

Siempre habrá lugar a elegir en medicina entre las concepciones más o menos clínico morfológicas y las basadas en la etio patogenia Lo más indicado parece combinar *en el mismo nombre* ambas características Desde el punto de vista terminológico hay dos soluciones posibles

— o bien decir como quería Kreibisch Prurigo Ekzem (en las lenguas latinas sería más vale eczema prurigo) agregándole el epíteto *atópico* para distinguirlo de las formas vecinas no atópicas

— o bien un poco en el sentido indicado por Jadasshon se reservaría el nombre de eczema exclusivamente para el eczema de contacto y se designarían las otras formas como dermatitis (atópica seborroide numular)

La noción de un *parenquima cutáneo* (Kromayer 1896) expresa la unidad funcional epidermis + cuerpo papilar sin tener en cuenta la clásica discriminación embriológica y habla en favor de un criterio funcional del eczema como una inflamación con un componente parenquimatoso dominante

Bajo este punto de vista el *eczema prurigo atópico* tipo Besnier Sulzberger y su variante no atópica numular son precisamente formas clínicas entre los eczemas y ciertas dermatitis intersticiales relativamente mas profundas

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EXPERIMENTAL BACKGROUND OF SOME ABNORMAL VASCULAR REACTIONS IN ATOPIC DERMATITIS AND SIGNIFICANCES OF SKIN TESTS IN MAN

by

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There are two main groups of pathophysiologic phenomena presented by cases of atopic dermatitis

1 A different dermal response from the normal physical stimuli

2 The formation of antibodies

I am here concerned primarily with the stigmata viz white dermographism The sweat retention syndrome—the antibody mechanism—will not be discussed The normal triple response occurring in healthy subjects displays a greater intensity in for example cases of urticaria factitia and where there is an increased basal metabolism

It is known that histamine is liberated by mechanical stimulation and that this substance is involved in the development of the symptoms The liberated histamine dilates the capillaries with a consequent increase in transudation and elicits a local nervous mechanism—the axon reflex (Lewis et Grant) The liber tion and elimination of histamine has been demons trated by estimation in normal skin and in wheals produced by a cratch inflicted with a match The histamine content in the stimulated area is reduced and a time factor is involved (Nilzen) In most cases of atopic dermatitis a red line is generally obtained 15 seconds after the skin has been stimulated and about 10 seconds later a white line appears owing to vasoconstriction No wheal is produced The reaction is thus quite different from that normally produced in the kin by stimuli of this type

The absence of reflex erythema shows that this abnormal reaction also appears after intracutaneous injection of hi tamine (Eyster et al) Norrlind has shown that in cases of Besnier s prurigo there is no halo after injection of protein antigen Lobitz and Campbell s discovery that intracutaneous injection of acetylcholine produced vasoconstriction in the area of a wheal underlines the difference in the type of reaction in the atopic skin It is interesting to note that acetylcholine administered to cases of atopy produces reflex erythema whereas histamine does not

Me surement of the skin temperature (I yster et al) has convincingly demonstrated such m_rked interference with the normal control that it must be ascribed pathogenic significance

This difference in response is undoubtedly due largely to contractility of the sm ll vessels Under normal conditions the capillaries do not contract there being no muscuar element proximal to the præcapillary sphincters (Chambers and Zweifach) The passage of blood through the capillaries is thus dependent entirely on whether or not the præcapillary sphincters are contracted There is however, a certain tonus in the endothelial cells which may have some significance

The muscular elements in the præcapillaries are very sensitive to biologically active substances such as adrenaline acetylcholine and histamine Changes in the electrolyte balance and the pH may influence the muscular activity of the præcapillaries

As already mentioned various biologically active substances undoubtedly have some part in the capillary activity in dermal process s such as inflammation mechanical trauma and antigen antibody reactions It may be inferred from the results of recent research that weak stimulus of the skin due to mechanical trauma gives rise to vasoconstriction lasting some minutes This effect is more pronounced in c_s s of chronic skin diseases such as seborrhœic dermatitis (Whitfield) (Kierland *et al*) This vasoc s-triction cannot occur in acutely inflamed skin (Whitfi ld) Rothman points out that the injection of low concentrations of epinephrine into the skin of healthy subjects elicits a response similar to the vasoconstrictior d e to weak stimulation

Where the skin is subjected to a more intensive mechanical stimulus vasodilatation (dermographia rubra) is produced it is also elicited by thermal and chemical stimuli This dilatation occurs in the smallest præcapill'a ies that have muscles and is accompanied by a secondary increase in the blood flow through the capillaries also At the site of this hyperæmic rea tion a wheal is produced by the extrusion of plasma through the walls of the dilated minute vessels The degree of these two effects depends on the intensity of the stimulus

Many substances eliciting similar responses on intracutaneous injection have the property of liberating histamine

Acetylcholine is regarded as one of the most important vasodilator metabolites in the skin and for this reason is considered to be one of the substances involved in the release of normal capillary reactions

What is the experimental evidence that histamine acetylcholine and epinephrine elicit the normal capillary reactions?

In brief

Histamine is liberated and eliminated from the areas stimulated O injection into the skin histamine elicits the triple response Antihistamines inhibit the triple response to some degree at least Moreover the mast cells are degranulated in the stimulated region (Drennan Asboe Hansen)

Acetylcholine is liberated likewise by mechanical stimulus of th skin and Dale considers that the substance is responsible for the arteriolar dilatation characteristic of the axon reflex flare Rothman et Coon have demonstrated acetylcholine in histamine wheals in man One type of pharmacologic effect that occurs in the normal skin when acetylcholine is injected intradermally

is the slow appearance of lasting redness The response increases in diameter as the acetylcholine diffuses into the tissues Atropine however does not seem to influence this vasodilator effect of acetylcholine to any extent That this alkaloid is however capable of inhibiting the vasodilator action has been pointed out by Armin et Grant

If highly diluted *epinephrine* is injected intradermally a blanching of brief duration is induced as on gentle stroking of the skin

As regards histamine if the abnormal response in cases of atopic dermatitis is examined in the light of the mechanism of the reaction of healthy persons the following conclusions might be reached

1 Histamine is not liberated on trauma at least not in such quantities as to be active

2 Histamine is liberated but either it is inactive or it is inactivated

3 Histamine is liberated but the tissue is resistant to its action

4 Histamine is liberated but the tissue reacts abnormally

There is no doubt at all that in normal subjects histamine is released on mechanical trauma This is borne out by the experimental results presented in Table I

TABLE I

Histamine content of the skin of healthy subjects after mechanical stimulation Excision after 10 minutes

CASE n	NORMAL SKIN		STIMULATED SKIN	
	Weight mg	Histamine m g	Weight mg	Histamine m g
1	67 3	18	69 8	5
2	60 0	2[illegible]	59 0	12
3	60 7	7	61 1	6
4	61 1	7	71 6	4
5	44 9	24	67 1	13
6	57 6	20	57 2	9
7	47 4	7	65 6	4
8	45 6	7	58 7	4
9	64 6	9	54 3	5
10	45 6	5	59 3	3
11	56 8	7	69 2	4
12	83 5	7	70 3	5
13	51 0	10	70 3	7

To ascertain whether histamine is liberated by mechanical stimulation of the skin in cases of atopic dermatitis also skin was excised from regions thus stimulated from regions situated 6 10 mm from the margin of the response elicited by the stimulus and from symmetrical unstimulated areas The excision was made with a punch and the same punch was used for each operation so as to obtain samples of skin that were roughly equal in area and weight Xylocaine without epinephrine was used as the local anæsthetic The *histamine* was estimated on surviving isolated small intestine of guinea pig according to Code

In cases of atopic dermatitis there was no reduction in the histamine content if the excision was performed within two to three minutes of stimulation but after 20 minutes an appreciable decrease was found Even when the histamine content was calculated in terms of dry substance the reduction was appreciable Table II

TABLE II

Histamine content of the skin of subjects with atopic dermatitis

CASE	EXCISION OF THE SKIN	UNSTIMULATED SKIN		STIMULATED SKIN		SYMMETRICAL UNSTIMULATED SKIN	
	min	Weight mg	Histamine microg	Weight mg	Histamine microg	Weight mg	Histamine microg
M B F	2 3	37 6	23	32 0	23	36 4	20
C M I	2 3	25 4	33	31 6	33	28 2	34
B G S	2 3	25 2	12	24 6	20	26 4	16
B G S	20	32 0	15	31 2	12	30 8	16
I J	10	35 2	27	45 0	13	38 8	29
M B F	20	26 8	15	24 2	9	26 0	18
I B	20	34 6	13	35 0	9	30 6	15
B H	20	30 8	38	32 2	18	33 2	34
P A P	20	26 0	30	27 2	14	25 8	28

From Table II it will be seen that the histamine content of the skin in patients with atopic dermatitis is higher than normal a result that may be ascribed to the inflammatory reaction

It is known that tissue histamine occurs chiefly in the mast cells To judge from several reports of studies on this subject this can probably be accepted as a fact To ascertain whether degranulation of the mast cells occurs in skin that has been subjected to mechanical trauma I stained a number of histologic specimens by Sylven s method That degranulation occured is indisputable and in some cases the effect was extremely pronounced It was detected in specimens taken within two to three minutes of stimulation This bears out the findings in the above histamine experiments The results of further studies on the mast cells in cases of atopic dermatitis will be published in due course It is unlikely that the released histamine is inactive nor does it appear to have been inactivated Skin from persons with atopic dermatitis seemed not to inactivate histamine in *vitro* In such a study I have used a method described by Granroth et Nilzen It is evident that histamine is not inactivated since wheals are produced on injection of this substane

The third possibility—that histamine is liberated but that the tissue is resistant to its action—is hardly acceptable for a number of reasons For instance vasoconstriction and wheals are elicited by various stimuli so that the organ cannot be regarded as resistant

The fourth possibility is more likely The experiments have not produced entirely convincing results however especially those tests in which the vascular mechanism was subjected to the action of various drugs

An abnormal liberation of epinephrine and acetylcholine may be consi

dered as one of the most likely possibilities Injection of epinephrine into the skin of atopic dermatitis cases produces no abnormal response but it is a known fact that in such cases the administration of acetylcholine produces a slowly spreading vasoconstriction—a delayed blanch (Lobitz and Campbell) Acetylcholine is therefore strongly suspected as a factor eliciting the abnormal vascular reactions Whether the epinephrine effect is involved in the acetylcholine action or whether this action is an abnormal phenomenon of the capillary system is still obscure

To judge from the results of several studies it is unlikely that hormonal influences have any determining role in these vascular reactions for instance hydrocortisone has no decisive effect on the immediate vascular reaction in the skin (Rajka 1958)

During 1956 57 Adams Ray and Nordenstam published some studies in which previously unknown cell systems were demonstrated in the dermal vessels These cells contain chromaffin granules and are generally located near capillaries

The second part of this lecture deals with the importance of skin tests and I have chosen to discuss the wheal reaction in atopic dermatitis I cannot mention all the authors who over the years have treated this subject If in clinical work one wishes to discover whether the wheal reaction is of significance in a disease it is not enough to perform a scratch test and then ask the patient whether symptoms have been obtained with one substance or another that has elicited a positive reaction The procedure to be followed will be of the following nature

1 Case history
2 Intracutaneous (scratch) test with reliable biologically standardized extract
3 Provocation or exposure test
4 Elimination observation
5 Specific anti allergic treatment observation

I have selected 24 cases of atopic dermatitis who gave a strong wheal reaction (+++) and I performed observations and treatment according the following plan

	ANTIGEN	CASE HISTORY	PROVOCATION EXPOSITION	EFFECT OF SPECIFIC TREATMENT	OTHER TREATMENT
Group I	Animal d nder	Positive 6	Positive 8	Good 4	Local 9
		Negative 4	Negative 2	None 6	None 1
Group II	Food	Positive 1	Positive 4[b]	Good 0	Local 6
		Negative 5	Negative 2	None 6	None 0
Group III	Pollen	Positive 6	Positive 4[a]	Good 6	Local 4
		Negative 2	Negative 4	None 2	None 6

Inh l t n of all rg n tra t o n al c t t d t ng obse at n
I t k of food d th ombo te ou t ot r t
Inh lati n nd observ t

None of these cases reacted with asthma after inhalation of extract or after contact with animals The positive provocation test was read on *the skin* the irritation increased there was manifest increase in erythema and œdema generally in the area of the skin already involved at the time of the test Controls with inhalation of dilutant alone were performed The increased activity of the skin appeared 1 6 hours following inhalation On exposure the symptoms appeared within one hour The two patients in question were however extremely sensitive to animals The pollen sensitive patients all presented increased reactions or reactions only during the pollen season The specific treatment was in most cases performed at the hospital with allergen injection every second hour and when the maximum dose had been given one injection every 3 4 weeks for at least one year and usually for three

I would point out that these 24 patients were selected from more than one thousand cases of atopic dermatitis tested at my laboratory I chose them because they had been carefully followed in order to show that testing and specific treatment can be of value

Have these patients now recovered completely? Six of the pollensensitive cases have done so but they may display a flare of eczema on close contact with pollen Of the patients who were sensitive to animals none recovered from their dermatitis but they could have contact with animals without reaction It would seem that the flexural skin is the shock organ of these patients as responses may be elicited there by systemic administration of antigen The typical prurigo picture is not evident after a provocation but prolonged contact with specific antigens however elicit skin eruptions of classic type Whether this occurs secondarily to scratching or not is difficult to decide but to judge from the conclusions of Rostenberg and others this is conceivable In my own opinion the antigen antibody reaction release biologic substances this giving rise in the shock organ to changes typical of the organ in question for instance for the epidermis cutis urticaria or dermatitis for the subcutis vascular impairment for the lungs asthma or infiltrations in the nose rhinitis It must be borne in mind however that it need not be a question only of antigen antibody reaction due to allergen of the food and pollen types infections too are an important factor Physical and other stimuli may also elicit typical allergic symptoms in the various shock organs

I will not pretend that atopic dermatitis—to say nothing of other allergic reactions of the atopic type—is due entirely to an antigen antibody reaction for then the morbid condition would be too simple but there are cases in which an antigen is playing so important a part in eliciting the symptom that it must be eliminated by one means or another I am in agreement with Rostenberg who writes I have yet to see one case in which I was convinced that a given protein allergen played a causal role But this is far from implying a rejection of the role of the allergen as the producer of the symptom I am therefore continuing to examine these cases from the allergen aspect and I believe I can make good use of this in the treatment of atopic patients

SUMMARY

The author discusses the signification of histamine and histamine liberation in the axon reflex He mentions that various biologically active substances have some part in the capillary activity in dermal processes such as inflammation mechanical trauma and antigen antibody reactions In the light of the research work up to this date he tries to explain the abnormal skin reaction after mechanical trauma in the skin of atopic patients The importance of histamine acetylcholine and epinephine in the skin reactions in atopic patients is discussed in detail

The author discusses also the importance of the immediate wheal reaction in atopic dermatitis He points out that in some cases the value of the skintesting is placed beyond doubt The author ends his lecture with the following words I will not pretend that atopic dermatitis —to say nothing of other allergic reactions of the atopic type— is due entirely to an antigen antibody reaction for then the morbid condition would be too simple but there are cases in which an antigen is playing so important a part in eliciting so the symptom that it must be eliminated by one means or another I am in agreement with Rostenberg who writes I have yet to see one case in which I was convinced that a given protein allergen played a causal role But this is far from implaying a rejection on the role of the allergen as the producer of the symptom I am therefore continuing to examine these cases from the allergen aspect and I believe I can make good use of this in the treatment of atopic patients

RÉSUMÉ

L auteur discute du role joue dans le reflexe d axone par l histamine et par sa libération

Il enumere les differentes substances biologiques actives exerçant une influence sur l activite capillaire au cours des processus cutanes tels que l inflammation les lésions mécaniques et les réactions antigenes anticorps

A la lumiere des resultats des recherches faites a ce jour il tente d expliquer les reactions cutanees anormales survenant chez les sujets atteints d eczema diathesique a la suite de lesions mecaniques L importance pour les reactions cutanees de l histamine de l acétylcholine et de l adrenaline chez les sujets « atopiques » est discutée

L auteur étudie aussi la reaction ortiee immediate dans l eczema diathesique Il indique que dans certains cas la signification des tests cutanes est ncontestable

L auteur conclut en ces termes « Je ne soutiendrai pas que l eczéma diathésique sans parler des autres reactions allergiques soit entierement imputable a une reaction anticorps antigene Ce serait la une maniere simpliste de considerer la maladie mais il est des cas ou l antigene joue un role si important comme responsable des manifestations pathologiques qu il importe de parvenir a l eliminer d une maniere ou d une autre »

Je suis d accord avec Rostenberg quand il dit « Il me reste encore a rencontrer un seul cas pour lequel je pourrais etre convaincu du role déterminant

joue par un allergène protéinique connu » Mais cela n implique pas loin de là la négation du role de l allergene en tant que responsable des symptomes pathologiques

C est pourquoi je poursuis l examen de trois sujets du point de vue de l action exercée par l allergene et pense pouvoir tirer de ces observations les enseignements utiles pour le traitement des malades « atopiques »

ZUSAMMENFASSUNG

Der Autor diskutiert die Bedeutung von Histamin und der Histaminfreisetzung in en Axon Reflexen Er glaubt dass verschiedene biologisch aktive Substanzen einen gewissen Einfluss auf die Kapillartätigkeit bei Hautprozessen wie Inflammation mechanischen Trauma und Antikorper Antigen Reaktionen ausuben Mit den bisher zur Verfugung stehenden Forschungsergebnissen versucht er die abnormale Hautreaktion nach einem mechanischen Trauma in der Haut atopischer Patienten zu erklaren Die Wichtigkeit von Histamin Acetylcholin und Epinephin fur die Hautreaktionen atopischer Patienten wird im Detail diskutiert

Der Autor diskutiert auch die Wichtigkeit der unmittelbaren Urtikaria reaktion bei atpischer Dermatitis Er stellt fest dass in manchen Fällen der Wert des Hauttestes uber jeden Zweifel erhaben ist Der Autor endet seinen Vortag mit den folgenden Worten Ich will nicht behaupten dass di atopische Dermatitis — von anderen Allergie Reaktionen des Atopie Typus ganz zu schweigen — nur von der Antikorper Antigen Reaktion abhangt, denn da wären die Krankheitsbedingungen zu einfach aber es gibt Falle in welchen das Antigen beim Hervorrufen der Symptome eine solch wichtige Rolle spielt dass es auf irgend eine Weise entfernt werden muss Ich stimme mit Rostenberg uberein der schreibt Ich muss erst einen Fall sehen bei welchen ich uberzeugt bin dass ein bekanntes Proteinallergen die auslosende Hauptursache darstellt Aber ich bin weit davon entfernt die Rolle des Antigens als Symptomerzeuger vollkommen zu verwerfen Ich setze daher weiter darin fort diese Falle vom Allergen Standpunkt aus zu untersuchen und ich glaube ich kann davon bei der Behandlung atopischer Patienten guten Gebrauch machen

RESUMEN

El autor discute la significación de la histamina y de la liberación de histamina en el reflejo axónico Menciona que varias sustancias biológicamente activas desempenan un papel en los procesos capilares cutáneos tales como la inflamación traumatismos y reacciones antígeno anticuerpo y trata de explicar a la luz de los conocimientos actuales la reacción cutánea anormal producida por trauma mecánico en la piel en pacientes atópicos Trata en detalle el papel de la histamina acetilcolina y epinefrina

El autor se refiere asimismo a la importancia de la reacción inmediata en la dermatitis atópica e indica que en algunos casos el valor de la testificación está fuera de toda duda Termina su exposición con las siguientes palabras No pretendo decir que la dermatitis atópica — para no citar

otras manifestaciones alérgicas atopicas — se debe enteramente a una reaccion antígeno anticuerpo lo cual sería una condicion mórbida muy simple pero hay casos en que un antígeno juega un papel tan importante que debe ser eliminado de una menera u otra Estoy de acuerdo con Rostenberg que dice tengo todas la que encontrar un caso en el cual pueda estar convencido que un antígeno proteico desempena un papel causal lo cual está lejos de excluir la posibilidad de que el alergeno produzca los síntomas Continuo por lo tanto a examinar todos los casos desde el punto de vista alergenico y creo que ello puede resultar de gran utilidad el el tratamiento de las dermatitis atópicas

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CLINICAL ASPECTS AND SKIN TESTS WITH VARIOUS GROUPS OF ALLERGENS INCLUDING THE ALLERGY TO INFECTIOUS AGENTS

by

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When discussing the clinical aspects and the role of allergic mechanisms in atopic dermatitis we must remember 1° that it is a disease in which multiple factors act in combination 2° that there is a high degree of uncertainty regarding the importance of the many trigger factors which the patients and the physicians find as causing the attacks 3° that it may be dangerous for the future research on atopic dermatitis if our attention becomes fixed on *one* factor in the etiologic complex

In other words [illegible]
it is important to [illegible]
of the many trigg [illegible]
uncertain and 3° that a narrow view upon atopic dermatitis as a purely allergic disease may lead to misconceptions in our approaches regarding the etiology and to mistakes and disappointment in the management of the disease

It is a matter of fact that many of these patients give positive reactions by skin tests with protein allergens—and often multiple reactions

The frequency of positive skin reactions in the many reports on lager patient materials varies rather much This cannot surprise when we consider that the frequency must depend upon technic upon the number of allergens employed upon the method of reading and evaluation of the reactions and also upon the age distribution within the patient materials

In my own investigations (1) I found positive skin reactions in approximately 10 p 100 of the patient from 1 to 5 years of age and in approximately 50 p 100 of the patients over 5 years of age It should be added that these figures are found by scratch technic

Whatever technic we use the essential question concerning the skin tests will be Do we find any conformity between the positive reactions and the clinical symptoms?

If we find conformity three new questions will arise 1° Can the allergens found by skin testing be the sole cause of the skin disease? Considering the many other trigger factors which act in atopic dermatitis the answer

to my opinion must be *No!* 2° *Does the skin condition disappear or improve when the suspected allergens are removed from the patient or the patient is removed from the allergens?* This question is very difficult to answer because of the fluctuating course of the disease After 15 years studying of atopic dermatitis I must say that I have never seen a case in which I was convinced that such procedures caused a *permanent* disappearance of the symptoms Sometimes however I found that it was followed by a temporary improvement 3° *Can the allergens found by skin testing cause unquestionable exacerbations of the skin symptoms when the patient is exposed to these allergens?* To my own experience Yes! —the itching may be aggravated but not very frequently and not regularly

The two main groups of allergens under consideration are *inhalants and food allergens*

INHALANTS

Considering this subject we must be aware of the frequent association of atopic dermatitis with asthma and hay fever We must realize that the positive cutaneous reactions to inhalants may very well be of clinical importance for the respiratory symptoms but of no value for the skin condition

1 Allergy to pollen — In my own examinations of patients with [illegible] positively to skin tests [illegible] 50 p 100 improved [illegible] became worse Th[illegible] patients who became worse during the pollen season again could be divided in two groups A Patients with aggravation of the skin condition [illegible] (50 p 100) B Patients with exacerbation of the skin symptoms together with attacks of hay fever (50 p 100)

Therefore to my opinion in some of the patients with positive reactions to grass pollen there is clinical evidence that the pollen allergy may explain some of the fluctuations in the disease

I should like to stress that the reactions to grass pollen in my hands always have been of the strongest type and that I do not remember to have seen false positive reactions to pollen extracts

Whereas pollen allergy in hay fever can be considered to be of definitive clinical significance in atopic dermatitis it can only be regarded as a single link in a chain of several etiologic factors

2 Allergy to molds — The problems of mold allergy have especially been investigated by *Feinberg* (2) who also investigated the occurrence of mold allergy in atopic dermatitis He found that patients with mold allergy sometimes suffered a flare up in what he called a mold season and he observed some patients with flare up during a strong wind resulting in a high number of mold spores in the air

As to the frequency of positive skin reactions with mold extract we must recognize that compared with the tremendous wealth of mold species those employed in skin testing will always be extremely small in number

In my own investigations on mold allergy I found that approximately 10 p 100 of the patients reacted positively to skin tests with extracts of the most common molds (especially *Penicillium Cladosporium Trichoderma* and *Aspergillus*) I tried to compare the occurence of these reactions with

the frequency of such living conditions which supposedly were favourable to growth of molds e g low sunless apartments dark rooms with damp wallpapers damp cellars under the apartments and houses in lowland areas with a high humidity in the air The frequency of positive reactions to molds however was approximately the same in patients living under such damp conditions as in patients living in dry houses

On the other hand many patients have told me that their skin condition improved by change from a damp to a dry environment and that they became worse on returning to damp surroundings

I am sure that all patients with atopic dermatitis do better under dry living conditions with a low humidity in the air but it is uncertain whether this beneficial influence of dry surroundings has anything to do with avoidance of molds

3 ALLERGY TO HOUSE DUST — The question of the significance of allergy to house dust is a matter of much controversy Most allergists claim that it is an important etiologic factor in asthma and they base their statements upon skin tests exposure tests by results obtained from specific desensitization and by improvement by use of allergen free rooms

The significance of house dust allergy in atopic dermatitis is much more difficult to evaluate Almost all patients with atopic dermatitis will improve under hospitalization under vacation or other forms of environmental change and almost all of them will suffer a relapse when they return to their original environment When we consider the high number of patients who improve by change of environment the frequency of positive reactions to dust extracts is surprisingly small In this respect I should like to mention that I have observed more false positive reactions with extracts of dust than with other inhalants and that real positive reactions only occured in patients who suffered from both asthma and atopic dermatitis

Furthermore I have never seen a patient with atopic dermatitis and asthma in which specific desensitization with extracts of house dust has influenced the skin condition—although it was said to have improved the asthma

Very often patients with atopic dermatitis and asthma must leave their occupation because their work is dusty but to my experience they always leave on account of their respiratory symptoms When they have left the dusty work their asthmatic attacks may stop whereas their skin disease is not influenced

4 ALLERGY TO EPIDERMAL ALLERGENS — In several patients with atopic dermatitis positive cutaneous reactions are obtained with allergens from domestic animals like horse dander horse hair dog hair cow hair cat hair and feathers

The frequency of reactions to cat hair is rather high and it is remarkable how rarely we find clinical evidence of hypersensitiveness In our department we have several times tried to give patients with strong positive skin reactions a living cat in their beds without aggravation of the skin symptoms

As to the hypersensitiveness to horse dander and horse hair there is more clinical evidence of its significance Some of these patients suffer a flare up of the itching when there is a high content of horse allergen in the air e g in circus when riding a horse or when working in horse stables For farmers with atopic dermatitis this form of allergy may sometimes be an occupational problem

Hypersensitiveness to feathers which is claimed to be of so great importance for asthma has in my own cases never been confirmed clinically For example I have never seen a patient whose skin disease became worse when we replaced a pillow containing kapok by a pillow containing feathers although the patient might have attacks of asthma

FOOD ALLERGY

Food allergy has been credited with much importance as an etiological factor chiefly based upon positive skin tests

Although it is rarely that I have found conformity between the positive skin reactions to food allergens and the clinical trial I will not go so far as *Cooke* (3) who says that he has never observed an exacerbation of atopic dermatitis from ingestion of that foodstuff which gave an immediate wheal reaction Especially I have seen some of the most severe allergic symptoms in patients with positive skin reactions to fish When these patients eat fish they may have generalized itching edema of the lips and the tongue and severe attacks of asthma

In other cases of food allergy as proved by skin testing it is extremely seldom to find conformity between the skin tests and the patients own experiences The patients may give a lot of positive skin reactions to food allergens but they have never themselves experienced any troubles by eating these special foods Conversely many patients will give information that they cannot tolerate special foods but skin tests turn out to be negative

In this connection I should like to say that I completely agree with Rostenberg jr (4) when he says that he is convinced that many individuals with this disease have iatrogenic allergies to foods it is that the knowledge of their hypersensitiveness is implanted in them by the physicians Very often when taking the story of such a patient he will mention that he cannot tolerate certain foods But by inquiring about the source of his allergic knowledge he will merely answer The doctor told me! , and a clinical trial will reveal that there is no food allergy a all

recognize it [illegible]

only certain dishes prepared with eggs (especially soft boiled eggs) [illegible] allergic symptoms in her child

Naturally it is important for our patients to avoid acute exacerbations but I have never observed that dietetic measures with avoidance of special foods influenced the chronic course of the disease neither when such measures were instituted by myself of by others And I have never observed any delay in the progressive improvement in hospitalized patients even though they received unrestricted diets all the time

BACTERIAL ALLERGY

The statements in the literature concerning the influence of infections on the course of atopic dermatitis are contradictory Some authors found that infectious diseases improved the skin condition and other reported that infections are accompanied by flare ups

The most thorough investigations in this field were made by Norrlind (5) who reported exacerbation of the skin symptoms in 39 p 100 of his patients in conjunction with infections in the respiratory system Most of his patients reacted positively to intracutaneous tests with bacterial allergens

My own experience on this subject is very limited Some of my patients have reported aggravation in conjunction with common cold and a few also in conjunction with other infectious diseases On no occasion did I see any improvement of the skin condition during the course of infectious diseases

In ten patients who suffered a flare up of the skin symptoms during common cold influenza and sore throats I performed cutaneous tests with extracts made by cultivation of bacteria from the throats By scratch technic I never found a positive reaction By intracutaneous technic however I sometimes found wheals which exceeded the size of the initial papule and the control papule but these reactions were always of the sluggish type i e they developed very slowly and they did not reveal the characteristics of really positive reactions

Some authors have reported that focal infections might play a role in atopic dermatitis These statements are based upon the therapeutic results by removal of the foci of infections I think that the fluctuating course of the disease makes it very difficult—not to say impossible—to attach any importance to the clinical significance of this kind of infections

Because of my own limited experience in this field I must cling to the great allergists and would like to quote Feinberg (2) who says At present only a conservative and guarded view can be taken of the entire subject of bacterial hypersensitiveness This was written in 1946 and although there has been done much experimental work since that time I think that his words have the same validity in 1958

Summarizing I must say that I have never found any conclusive proof that a single allergen or a special group of allergens can be considered as the sole cause of atopic dermatitis and nor I have found conclusive proof that exposure to the allergens named or avoidance of these allergens can definitely influence the chronic course of the disease

It is a matter of fact however that most of the patients with atopic dermatitis do react positively to various groups of allergens and often to multiple allergens but if we are to be honest in our studies we must recognize that we have overwhelming difficulties in bringing the clinical aspects into agreement with the positive and negative skin tests

According to Hellerstrom (6) the high frequency of positive cutaneous reactions signifies that patients with atopic dermatitis are sensitization machines always ready to be sensitized to new allergens the amount and nature of which we do not know and cannot prove in many of the patients—neither by skin tests nor by clinical trials

In closing I should like to mention the possibility of sensitization to substances from the patients own skin Such substances may derive from the dander from the sweat or from other of the structures associated to the skin Simon (7) has demonstrated that human dander often produces positive reactions in individuals with atopic dermatitis I have been able to confirm his results (1) but in most cases it is only possible to elicit the reactions by patch tests or by scratch patch tests and the reactions are of another character than the acute whealing reactions and the patch test reactions of contact type

In this connection it should be remembered that patients with atopic dermatitis often have an ichthyotic or at least a very dry skin According to Rothman (8) the main physiologic disturbance in ichthyosis is an inhibition of the normal shedding The horny layers of epidermis do not separate into single cells but is piled up so that the horny layer becomes several times thicker and more compact than normal

If in patients with atopic dermatitis there is an inhibition of the normal shedding with consequent thickening of the horny layer and if the patients are allergic to protein allergens in their own horny layer we may reach o the concept—although at present merely speculative—that the persistent scratching continuously will bring about a production of allergens which steadily will elicit numerous reactions in the skin of the type described by Simon (7) in his scratch patch tests with human dander

This concept could very well be combined with Sulzberger s theories concerning the sweat retention syndrome as an essential factor in the pathogenesis of the disease (9)

If this concept should prove to be correct we might have a pathway for explanation of the favourable effect of tar with its correcting action upon abnormalities in keratinization and the favourable effect of prevention of scratching

SUMMARY

The article discusses the frequency of positive reactions by skin tests with protein allergens in patients with atopic dermatitis and the occuren e of conformity between these reactions and the clinical symptoms

In patients allergic to grass pollen there is some clinical evidence that pollen allergy may explain some of the fluctuations in the disease

Although many patients give positive reactions to skin tests with mold extracts and improve under dry living conditions the connection between mold allergy and the beneficial influence of dry surroundings is uncertain.

Allergy to dust may play an important role for the frequent asthmatic attacks in patients with atopic dermatitis but it cannot be proved to be of clinical significance for the skin condition

Conformity between the positive skin reactions to epidermal allergens from domestic animals and aggravation of the skin symptoms when the patients are exposed to these allergens can only be found in a few patients with allergy to horse dander

Among food allergies allergy to fish may — although rarely — be the cause of severe aggravations of the itching Otherwise the clinical signi

ficance of food allergy seems to be somewhat exaggerated and — especially — dietetic measures cannot influence the chronic course of the disease

[illegible]

At last the possibility of sensitization to substances from the patients own skin is discussed

RÉSUMÉ

L auteur discute dans ce travail de la frequence des reactions positives des tests cutanes pratiques avec des allergenes proteiniques chez des malades atteints d eczema diathesique et de leur concordance avec les symptomes cliniques

Certaines donnees cliniques permettent de penser que l allergie due aux pollens peut expliquer certaines phases de l evolution de la maladie

Bien que beaucoup de ces malades reagissent positivement aux tests cutanes pratiques avec des extraits de moisissures et que leur etat s ameliore lorsqu ils vivent dans une atmosphere plus seche les rapports entre l allergie aux moisissures et l influence d une ambiance seche ne sont pas etablis

L allergie a la poussiere peut avoir une influence importante sur la frequence des crises asthmatiques des malades atteints d eczema diathesique mais il ne peut etre prouve qu elle ait une importance clinique directe sur l affection cutanee

La concordance entre les reactions cutanees aux phaneres d animaux domestiques et l aggravation des symptomes cutanes lors de l exposition du malade a ces allergenes ne se rencontre que chez quelques sujets allergiques aux squames de cheval

Parmi les allergies alimentaires l allergie au poisson peut bien que rarement provoquer une aggravation serieuse du prurit D autre part la signification clinique des allergies alimentaires semble quelque peu exageree et il ne semble pas plus particulierement que les regimes puissent influencer le cours chronique de la maladie

L influence des infections sur l eczema diathésique est douteuse et les reactions cutanees aux allergenes bacteriens ont loin d etre certaines Il faut pour ces raisons avoir une opinion réservée sur l hypersensibilisation bacterienne

Pour terminer les possibilites de sensibilisation par des substances produites par la peau meme du malade sont discutees

ZUSAMMENFASSUNG

Der Beitrag behandelt die Haufigkeit von positiven Reaktionen von Hauttests mit Protein Allergenen bei Patienten mit atopischer Dermatitis und das Vorkommen einer Uebereinstimmung zwischen diesen Reaktionen und den klinischen Symptomen

Bei gegen Graspollen allergischen Patienten bestehen einige klinische Beweisgrunde dass die Pollenallergie manche der bei dieser Krankheit auftretenden Schwankungen erklaren konnte

Obwohl viele Patienten positive Hautreaktionen bei Testen mit Schimmel

textrakten geben und sich bei trockenen Lebensbedingungen bessern ist der Zusammenhang zwischen Schimmel Allergie und dem bessernden Einfluss einer trockenen Umgebung noch ungewiss

Allergie gegen Staub durfte eine wichtige Rolle bei den haufigen Asthmaattacken bei an atopischer Dermatitis leidenden Patienten spielen es kann aber nicht bewiesen werden dass sie fur Hautbedingungen von klinischer Bedeutung ist

Uebereinstimmung zwischen positiven Hautreaktionen epidermischer Allergene von Haustieren gegenuber und der Verschlimmerung der Hautsymptome wenn diese Patienten diesen Allergenen ausgesetzt werden kann nur bei wenigen Patienten mit einer Allergie gegenuber Pferde Schuppen gefunden werden

Bei den Lebensmittelallergien kann Fisch wenn auch selten die Ursache einer Verschlimmerung des Juckens sein Andererseits durfte die klinische Bedeutung der Lebensmittelallergie etwas ubertrieben sein und — besonders — Diatmassnahmen konnen den chronischen Verlauf der Erkrankung nicht verhindern

Der Einfluss von Infektionen auf die atopische Dermatitis ist zweifelhaft und Hautreaktionen gegenuber bakterieller Allergene sind nicht zuverlassig Eine gewisse Skepsis muss daher einer bakteriellen Ueberempfindlichkeit entgegengebracht werden

Zum Schluss wird die Moglichkeit einer Sensibilisierung gegen Substanzen von der eigenen Haut des Patienten diskutiert

RESUMEN

El autor discute la frecuencia de reacciones positivas en la testificación con alergenos proteínicos en enfermos de dermatitis atopica y la coincidencia entre los resultados y los síntomas clínicos

En pacientes con fiebre de heno hay alguna evidencia de que esta enfermedad puede explicar algunas fluctuaciones de la dermatitis En el caso de pruebas positivas a hongos la vinculación es muy incierta aunque estos pacientes se benefician en un ambiente seco La sensibilización al polvo deméstico tiene una gran importancia en el curso del asma en los paciente que tienen además dermatitis pero no se ha podido demostrar la influencia de este alergeno sobre la enfermedad de la piel La coincidencia entre reacciones positivas a epitelios animales y la peoría de las dermatitis cuando los pacientes se exponen al correspondiente alergeno sólo ha podido ser encontrada en unos pocos casos de alergicos a caspa de caballo Entre las alergias alimentarias la ingestión de pescado puede ser causa aunque raramente de severas recidivas del prurito por lo demas el significado clínico de la alergia alimentaria ha sido muy exagerado y en especial los recursos dieteticos que no influyen en el desarrollo cronico de la enfermedad La influencia de las infecciones es dudosa y las reacciones cutáneas a alergenos bacterianos son de poco valor

El autor discute finalmente la posible sensibilizacion a sustancias de la propia piel del paciente

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DIAGNOSTICO Y TRATAMIENTO DESDE EL PUNTO DE VISTA *ALERGICO CONSIDERACIONES SOBRE* EL MECANISMO REAGINICO Y POSIBLES IMPLICACIONES DE REACCIONES ASOCIADAS DEMORADAS

por

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La dermatitis atópica es una manifestacion cutánea primordialmente de naturaleza alérgica aunque puede estar influenciada por factores locales por circulos viciosos creados por la enfermedad en si y que influyen en parte en su cronicidad El maximo esfuerzo debe dirigirse a desentranar su mecanismo intimo y a enjuiciar aquellos hallazgos inmunologicos y factores locales asociados que permitan un enfoque terapeutico mejor El estudiar una dermatitis atopica sin adentrarnos en el factor inmunologico es lo mismo que estudiar una tuberculosis sin considerar la hipersensibilidad de infeccion

Su asociación frecuente a otras manifestaciones de hipersensibilidad y a las respuestas humorales y celulares que la acompañan son hechos que por su frecuencia no pueden ser considerados como simples coincidencias sin real significación como algunos han desafortunadamente pretendido hacer Me refiero por supuesto a la presencia de reaginas en la sangre circulante y al aumento de eosinofilos que casi constantemente la acompana y que no representan otra cosa que respuestas netas a estimulos antigénicos y que hace pensar que el cuadro clinico está en relacion estrecha con un mecanismo inmunoalérgico aunque no sea por intermedio directo del anticuerpo sensibilizante de piel La herencia de la predisposicion atópica y la frecuencia de su asociación con manifestaciones de este tipo como el asma y las rinitis alérgicas da mas peso a este enfoque conceptual Las dos terceras partes de estos enfermos tienen antecedentes familiares positivos La dermatitis aparece a veces muy precozmente En los primeros dias de la vida en el 15 p 100 de los casos en las primeras semanas en el 35 p 100 y en un 50 p 100 despues del primer año segun nuestras estadisticas

Dejando a un lado varios aspectos que se salen del marco de mi presentación como son las caracteristicas anatómicas de las zonas donde aparece la influencia del mecanismo sudoral del rascado de la mayor o menor locali

zacion de anticuerpos en distintos sitios de alteraciones de los reflejos axónicos de la influencia de las irritaciones y contaminaciones cutáneas y de las distintas otras causas que han sido consideradas por los otros panelistas voy simplemente a concretarme a los hallazgos inmunológicos encontrados y a su interpretacion

Los factores nerviosos asociados (que influenciaron la creación del erroneo nombre de neurodermatitis aun tan en boga por algunos) no constituyen factores causales primarios y no explican entre otras cosas la respuesta inmunológica asi como tampoco los brotes en los niños recien nacidos

Muchos de estos simplemente se explican por el hecho de aumentar la vascularización modificar el umbral del prurito e influenciar la sudoracion la cual de por si actuaría como si minusculas inyecciones intradermicas ocurrieran al mismo tiempo especialmente cuando los conductos sudoriparos están obstruidos por la lesión anatómica como *bien ha señalado* Sulzberger Es de señalar como estos enfermos cuando tienen la piel sana sudan libremente sin presentar prurito y sin exacerbarse el cuadro Es de considerar igualmente que el sudor puede contener cierta cantidad de alergenos o ser irritante por su composición

Es importante en las dermatitis conside ar el papel jugado por el síndrome de retencion sudoral Igual que hay asmaticos taponados tenemos un taponamiento en las dermatitis En ocasiones una avitaminosis A producida por la dieta restringida empeora el cuadro al producir o favorecer el taponamiento como hemos tenido la oportunidad de comprobar histológicamente

Esta presentación esta basada en el estudio de varios centenares de casos de dermatitis atópica estudiados en los ultimos veinte años y en particula de cincuenta casos que como requisito tenían el de habérsele hecho cuando menos una transferencia pasiva en el transcurso de su estudio lo cual era de importancia primordial

En algunos casos hemos tenido la oportunidad de estudiar su respuesta reagínica en distintos períodos separados por años entre si y valorar los distintos factores que han intervenido en el cuadro clínico

Por ello y con fines de un mejor estudio se hicieron un buen numero de experiencias con el fin de eliminar una serie de posibilidades que fueron considerándose y asi dejar aclaradas ciertas dudas Estos fueron los siguientes

1 Tests intradermicos repetidos en el mismo sitio en dias sucesivos tratando de reproducir las lesiones
2 Idem asociando el alergeno con distintas grasas
3 Inyeccion en sitios donde se produjo antes o conjuntamente una reacción bacteriana
4 Inyeccion de copulados con precolageno y proteinas globulosas
5 Titulación de reaginas neutralización y busqueda de anticuerpos bloqueadores
6 Irritación de sitios en los cuales se produjo un habón
7 Pruebas de contacto
8 Transferencias pasivas pruebas de agotamiento de reaginas y pruebas cruzadas
9 Pruebas de parche escarificacion e intradermoreacción en flexuras y en otros sitios

10 Transferencia de reaginas a sujetos atópicos
11 Pruebas de provocación con los presuntos alergenos encontrados
12 Estudio relativo entre la intradermoreaccion transferencia pasiva y repetición y supresión del contacto
13 Estudio histopatologico en los distintos periodos y lesiones
14 Estudio electroforetico de los sueros tanto de proteinas como de lipidos

Hay distintos puntos de vistas en relacion a la teoria reaginica que pudieramos dividir en la forma siguiente

1 Los que le dan todo el valor a la presencia de la reagina y consideran que este es el anticuerpo que influye en la reaccion
2 Los que le niegan todo valor
3 Los que ni siquiera consideran esta dermatitis en el grupo de las atopias
4 Los que creen que hay otro factor inmunologico además de la reagina Creemos que nuestro deber es valorar eclecticamente las distintas observaciones para llegar a una conclusion que nos satisfaga y permita en una buena parte explicar la razon de un buen numero de discrepancias nacidas principalmente de enfocar unilateralmente el problema y otra de causas reales como son

En favor del mecanismo reaginico

a La presencia casi siempre en la sangre de estos anticuerpos
b La demostración en muchos casos de que el alergeno productor de la reagina era el mismo que producía la dermatitis
c Su supresion en ellos coincidia con la regresión del cuadro

En contra de dicho mecanismo

a La no coincidencia entre la reagina y el cuadro clinico en otros casos aunque se pudiera explicar el de las otras atopias asociadas
b La inocuidad del alergeno en muchos casos el cual era perfectamente tolerado
c Ausencia de la reagina en algunos enfermos pudiendo incluso exacerbarse o producirse la dermatitis por algunos alergenos que no reaccionaron.
d La no producción de la dermatitis por inyección intradérmica del alergeno tanto en zonas lesionadas como en las sanas

Para poder contestar de una manera concreta las anteriores discrepancias compararemos en todos los enfermos estudiados el resultado de la transferencia pasiva con las observaciones clínicas para de una manera estadística poder enjuiciarlo antes de pasar a nuevos enfoques

Sabemos que las reacciones atopeno reagina se caracterizan primordialmente por la aparición de una *reaccion inmediata blanda evanescente en forma de habon urticariano* que pudiere considerarse como la lesión elemental aunque ese no sea al unico mecanismo por el cual se produzca el habón ya que por liberación de un mediador especialmente histamina o substancias afines puede producirse sin tener que haber una reacción A A previa.

Esta es el tipo de reacción que encontramos por ejemplo en la riniti a polenes o inhalantes En la dermatitis atopica no ocurren ronchas urticarianas y es discutible que la reacción mínima elemental sea un habon subclinico En cambio si el enfermo tiene una atopia respiratoria sobreanadida aqui si sus mucosas presentaran un edema Por cierto ya que hablamos de mucosas es de recordar que no ocurren lesiones mucosas en los sujetos afectos solo de dermatitis atópica y en cambio si ocurren cambios en el cristalino en el 8 % de los casos I as lesiones de la dermatitis atopica tienen la caracteristica de ser mas *lentas en su desarrollo y desaparicion son duras y no evanescentes* Es lógico que asi sea pues su componente celular es más marcado que en el habón Esta diferencia anatómica entre ambos tipos es muy reta y ello hace pensar que su mecanismo de producción es distinto aunque ambas reacciones se inicien en el corion

En los casos estudiados encontramos como datos de interes lo siguiente que el 80 % tenian reaginas circulantes el 58 % las tenian a alimentos otro 58 % a polvo de casa el 26 % reaccionaron a otros inhalantes distintos al polvo principalmente a tabaco y el 18 % reaccionaron a caspa o pelo de animales El 86 % tenian eosinofilias marcadas La presencia de reaginas po iblemente coincidía con la causa en un numero mayor que en aquellos en que no aparecía

Su hallazgo permite en muchos casos aclarar un diagnóstico de una causa que no se había so pechado, lo cual ya hace que el valor de estas sea grande especialmente cuando se trata de inhalantes y aunque no sea el anticuerpo productor directo de la reaccion En otros casos los tests eran negativos v pudo comprobarse la sensibilidad clinicamente En ocasiones no se encontraton reaginas a un alergeno determinado y después de un tiempo si aparecián siendo esto mucho mas frecuente que lo inverso En algunos casos pudimos observar una variacion en la respuesta reaginica asociada siempre a nuevos contactos siendo esto de gran importancia pues no se debe basar un diagnóstico en tests hechos dos o tres años antes aunque en muchos casos coincidieren

En la mayoria de los casos hay reaginas y su presencia permite en muchas ocasiones conocer la causa etiológica aunque en otros no tengan relacion clinica o solo expliquen los sintomas respiratorios En ocasiones se descubre por medio de dietas el efecto provocador de un alimento y los tests intradermicos directos y pasivos son negativos

Todo nos hace pensar que debe haber otro factor en juego que debe ser considerado muy minuciosamente

Podria ser por otro mecanismo immunológico como incluso ha sido sospechado en ocasiones o llamándosele el factor X (para algunos diatesico) y que a nuestro juicio como veremos mas adelante parece estar condicionado a la posible presencia de anticuerpos celulares producidos por fracciones antigenicas lo que explican mejor el tipo de reaccion demorada que se observa

La reagina vendria a representar simplemente la respuesta general del atopico a la sensibilización espontanea con alergenos Para que presente una dermatitis seria necesaria la concurrencia del otro mecanismo

Al principio creíamos que habia dos tipos de reacciones entremezcladas entre si una reaccion rápida causada por la reagina y una lenta debida a un factor bacteriano que hacía adquirir caracteristicas demoradas a la

reacción tisular Esto lucía logico por la aparente relacion que hay en algunos casos en los cuales un factor bacteriano intestinal produce flare up de las dermatitis

Las inyecciones combinadas de alergenos y germenes de las flora intestinal cutanea o bronquial no reproducen las lesiones ni se comportan de una manera distinta que en los sujetos normales

El factor local infeccioso secundario tiene un efecto mantenedor si se quiere pero nunca es el causante inicial No se ha podido demostrar que ocurra una reaccion demorada por hipersensibilidad bacteriana asociada

El rascado actua secundariamente aumentando y extendiendo el dano histologico inicial haciendo aparecer papulas y produciendo una liquenificacion secundaria

Esta ultima aunque aparece en la dermatitis atopica no constituye una lesión inicial ni es específica En contra de la teoria de que el rascado es lo que produce la dermatitis lo tenemos en la aparicion de lesiones papulosas e incluso vesiculosas sin intermedio del mismo y ademas que en otros atopicos como son los asmáticos puros el rascado no la produce que no por eso dejan de ser diatésicos si se quiere usar este termino que indica siempre algo generico y no privativo del enfermo con dermatitis

Es debido al rascado en gran parte la diferencia que notamos en el aspecto macro y microscopico de las lesiones en un buen numero de casos o sea que modifica el aspecto pero no puede ser la causa original Es simplemente un eslabon en la cadena de hechos La localizacion típica parece estar en relación con ciertas caracteristicas de estas zonas grueso de la capa cornea vascularización *pH* distribucion de las glandulas humedad movilidad asi como quizás a otros factores que desconocemos

La dermatitis atópica generalmente precede a las otras manifestaciones de hipersensibilidad en el mismo individuo en el 82 % de nuestra causistica

Hace anos se consideró que el mecanismo de la dermatitis atopica estaba explicado por la interreaccion entre la reagina y su correspondiente atopeno y durante muchos anos este ha sido defendido por la mayoria de los alergistas ya que en muchas ocasiones hay coincidencia entre la reagina y la causa de la dermatitis pero como en otras esto no ocurre y no aparecieron reaginas circulantes habia que analizar el problema más de cerca y buscar la explicación La reagina como sabemos se caracteriza por sensibilizar la piel y dar lugar al combinarse con el alergeno a liberación de substancias histaminoideas con formacion del habón típico que es lo que encontramos al hacer los tests directamente en la piel del paciente con dermatitis atópica pero no espontaneamente Esta ausencia de ronchas podría pensarse que es debido a causas inherentes a los tejidos de shock que no responderían formando habones Esto no es asi ya que cuando inyectamos el alergeno productor de la reagina o simplemente lo aplicamos en lesiones abiertas estas responden con un habon y lo mismo sucede con histamina Esto excluye el que haya un factor local inhibitorio que impida la formacion del habón En cambio la ingestion de un alimento determinado puede exacerbar las lesiones como en multiples ocasiones hemos hecho lo cual está en favor de su especificidad

Como vemos la teroia reagínica falla de explicar algunos aspectos especialmente el distinto tipo de reaccion la no produccion de la lesion por inyección intradérmica y el haber dermatitis con reaginas sin significación

clinica y otros en las cuales no aparecen lo que nos obliga a considerar otros mecanismos que pudieren ser

1 Por formarse otra reagina a una fracción del alergeno original como ha sido demostrado por Cooke con proteosas de leche en otro tipo de alergias pero que lo excluimos aquí porque lo que se produciría sería otra reagina y esta no permite explicar todo el mecanismo

2 Que el alergeno o una fracción del mismo se haya copulado con proteinas fibrosas y que ese nuevo alergeno fuere el productor de un anticuerpo celular en la forma señalada por Mayer para explicar el mecanismo de las reacciones de contacto a productos químicos No parece que esto sea así por el hecho de no ocurrir sensibilización epidérmica al mismo alergeno En las experiencias practicadas con este fin no pudimos obtener reacciones positivas del tipo de la dermatitis inyectando alergenos combinados con precolágeno Pudiere pensarse en la posibilidad de que otros componentes influyan haptenicamente

3 Porque se haya formado en el curso de la degradacion del alergeno otro anticuerpo con un comportamiento o característica distinta para no prejuzgar sobre su naturaleza pero que tendria que ser un anticuerpo celular ya que las reacciones observadas en la dermatitis son del tipo demorado y no son lo evanescentes y blandas de las reacciones de la urticaria El anticuerpo celular estaria localizado en las celulas del reticulum vascular del corion superior

Si tal hipotético anticuerpo celular fuere la explicacion habria que considerar que en una proporción de los atopicos (aquellos con dermatitis) puede ocurrir en ciertos momentos una sensibilizacion doble una con respuesta de reaginas (que explicarían las reacciones tipo habón como son las manifestaciones respiratorias) y otra con respuesta de anticuerpos celulares fijos producidos por productos de degradacion del alergeno Sería como si este grupo de atópicos dobles (del aparato respiratorio y de la piel) pudieran manufacturar otros anticuerpos Indicaria una expresion de hipersensibilidad o reactividad mayor Esto a la luz de una hipótesis luce factible y permite explicar el por que las reacciones de la dermatitis atopica son de distinta consistencia y caracteristica tisular el por que son demoradas el por que no se reproducen por inyeccion intradermica del alergeno el por que pueden coincidir o no con la reagina y el por que solo aparecen cuando el contacto desencadenante se hace por unas vías y no por otras Esto puede tener ciertos puntos débiles si se quiere puede incluso objetársele que hay que demostrar que existe tal anticuerpo celular lo cual no prueba nada ya que hay multiples ejemplos similares de mecanismos que solo se pueden explicar hipoteticamente y no por ello han dejado de exponerse cuando no se encuentran explicaciones claras Pensamos que la diferencia entre la dermatitis de contacto y la atopica en relación al anticuerpo celular es que en la primera son las células epidérmicas las sensibilizadas mientras que son las del endotelio vascular y del corion vecino las que contienen el anticuerpo fijo en el segundo caso Por ello aunque son reacciones demoradas ambas no aparecen conjuntamente y ademas los alergenos que actuan en la dermatitis atopica no son del mismo tipo ni han sensibilizado por la misma via

Volviendo a las caracteristicas histologicas de las reacciones tipo habon y a las de dermatitis atópica encontramos ciertas diferencias aunque sin

querer por ello darle un valor absoluto Para incurrir en un error menor voy a comparar solo el cuadro histológico del corion de un habón alergico con una lesión reciente de dermatitis En el primero lo que lo caracteriza es la dilatación de los capilares exudacion de liquido de edema y acumulacion de eosinofilos perivascularmente En el segundo encontramos como vemos en los slides un engrosamineto de las paredes vasculares aumento de las celulas adventicias infiltración perivascular principalmente de linfocitos histiocitos y algunos eosinofilos los cuales incluso pueden estar ausentes El que la dermatitis atópica tenga un componente celular mas marcado y distinto a la lesion tipo habón está más en favor de un mecanismo de reaccion más en consonancia con una reaccion demorada celular Es de señalar como ha sido demostrado por Rapapport que hay una depolimerizacion de la substancia amorfa con mala tinción y adelgazamiento de la membrana basal la cual igual que los fibroblastos e histiocitos se tiñe mal

Si el hipótetico anticuerpo celular fuere producido por el alergeno original y no por una fracción del mismo es lógico que habría una reacción al ponerlos en contacto lo cual no ocurre ya que la inyeccion intradermica a distintas profundidades nunca reproduce la lesion y tampoco cuando hemos tratado de mantener el alergeno in situ por medio de retardantes Las experiencias hechas por reabsorción transepidérmicas hechas por otros investigadores han dado resultados muy disímiles Tampoco ha sido posible producir la lesion inyectando suero conteniendo alergeno obtenido postpandrialmente pero aqui la reacción serica local le quitó valor a la prueba El hecho de que solo se haya podido especificamente reproducir la dermatitis y empeorarla por la ingestión o inhalación de algunos alergenos nos esta indicando que la via de introduccion tiene mucho que ver Esto favorece la hipótesis de que el alergeno ha debido sufrir una transformacion en el organismo necesaria a la reaccion Un alergeno al estimular los sitios de formacion de anticuerpos no tiene necesariamente que producir un solo anticuerpo con un unico comportamiento multiples son los casos como veremos mas adelante en que en el mismo organismo animal o humano pueden en ocasiones aparecer más de uno o uno solo con distintas afinidades o comportamiento especialmente cuando el alergeno es muy potente o el sujeto muy reactivo Si dicho supuesto anticuerpo se formare por la estimulación de los centros anticuerpos formadores por otras fracciones o productos de degradación de este podría aparecer conjunta o independientemente con la reagina Lo que si tendria que poseer es una característica celular fija Quizás especulativamente pudieramos decir que por no ser detectable en el suero tiene que ser distinto a las precipitinas y por lo tanto a las reaginas lo cual concuerda perfectamente con la clínica

Que el atopico tenga reaginas en cantidad es simplemente la expresión de su facilidad en sensibilizarse y dar lugar a alergias del tipo inmediato Que por ser atópico y producir respuestas de anticuerpos y celulas de extirpe alergica es un indicio más de su facilidad para crear anticuerpos

Es de interés señalar que la via por la cual se hace la sensibilizacion tiene una gran importancia en la producción de uno u otro anticuerpo

Es por ello que si inyectamos a un atópico y lo cual ocurre tambien a los individuos normales un alergeno por ejemplo un extracto de polen o simplemente polvo de casa produciremos un anticuerpo termoestable distinto a la reagina y sin poder sensibilizante de la piel Este anticuerpo que

como sabemos es una de las explicaciones al resultado beneficioso de la vacunación no se produce espontáneamente en el individuo En cambio si la sensibilización se hace espontáneamente a través de las mucosas intestinal o respiratoria se producirá una reagina No vamos a entrar a discutir las teorías que tienden a explicar esta diferencia aunque si es de importancia recordar que si el antígeno a inyectar es de gran poder sensibilizante como sucede con los extractos de ascaris lumbricoides si se produce una reagina Queremos igualmente señalar que en ciertas parasitosis con producción de reaginas y cuadros clínicos de alergias como es el caso de la fasciolasis hepática no es solo la reagina el anticuerpo que se descubre ya que también una precipitina aparece en el suero aunque no tenga la misma especificidad de la reagina Los distintos anticuerpos tienen una localización distinta en las globulinas así por ejemplo en las precipitinas animales están localizadas a la gamma globulina e igualmente lo está en ella el anticuerpo bloqueador mientras que la reagina tiende a aparecer más en la beta globulina aunque pueda encontrarse tambien en las otras fracciones

Estudianto electroforeticamente los sueros de enfermos con dermatitis atopica en fases agudas y en períodos de remisión parece que hay cierta diferencia en algunos casos con tendencia a elevarse la beta globulina con disminución a cifras normales cuando el enfermo ha mejorado o limpiado sus lesiones

Sin querer darle aun un gran valor pues necesita una mayor comprobación esto pudiere interpretarse como una respuesta alta de anticuerpo [illegible] haciendo
que en dicho c [illegible]
electroforesis d [illegible]
terol con norr [illegible]
modificarse

Algunos llegan hasta a despreocuparse de los tests lo que es algo inexplicable pues en el peor de los casos estos nos ayudan a conocer la causa del asma o de la rinitis que tambien puede sufrir nuestro enfermo y ya conocemos como alternan o se suceden ambas manifestaciones en el transcurso de su vida El considerar solo el aspecto cutaneo y no el general de un atopico es solo tratarlo parcialmente y olvidar que nuestro enfermo puede tener un cuadro alergico pulmonar conjunta o posteriormente

Cuando los tests son negativos (lo cual realmente es la excepción en nuestra casuística) y el enfermo enfáticamente comprueba que un alimento o el contacto con ciertos inhalantes lo empeora y produce brotes hay que buscar la explicacion en otro mecanismo immunológico Esto sucede principalmente en casos de alergia alimenticia Quizás el alergeno al metabolizarse experimenta modificaciones y sean fracciones del mismo las que actuen. Esto es por supuesto más frecuente en el caso de los alimentos aunque no tengan necesariamente que producir anticuerpos celulares que no tienen por que aparecer en otros cuadros

En ocasiones el contacto local no por inyeccion produce reacciones edematosas lo cual concuerda con la presencia de reaginas pero en ocasiones esto ha sido seguido de lesiones generalizadas de dermatitis especialmente cuando el contacto se ha hecho sobre areas no cicatrizadas y usando alergenos muy potentes como es la clara de huevo Pero lo que más frecuentemente vemos es una reacción edematosa en el lugar del contacto por polvo o por huevo sin reproducir la dermatitis Cuando la piel está perfectamente

sana no ocurre esta penetración transepidérmica lo cual hace pensar que en los casos de lesiones descubiertas estos alergenos producen una reactivación o empeoramiento de las lesiones ya que vendría a ser como si multiples escarificaciones se estuvieren repitiendo casi constantemente

Es por ello que debe buscarse una rapida cicatrización y evitar el contacto directo con alergenos Las pruebas de parche a otras substancias que muchos dicen ver con mayor frecuencia en estos casos no las vemos excepto si se quiere las producidas por la caspa humana y por la lana Quizás la sensibilización a sales metálicas pueda ser más frecuente pero la proporción general de dermatitis de contacto nos parece inferior a las de los grupos controles

Hay algo a senalar y es que en ocasiones cuando cubrimos una buena parte de las lesiones parece que las que dejamos descubiertas tambien mejoran como si dependieren de una menor reabsorción de alergenos Además estamos evitando el rascado que es de por si la causa que más importancia tiene en sta enfermedad fuera del prurito por irritación de las terminaciones nerviosas causado por el daño celular Muchas veces el daño celular minimo no llega a exteriorizarse en forma de pápulas o vesiculas si impedimos el rascado

La aparición de la dermatitis precozmente en los recien nacidos hace pensar que estos fueron sensibilizados in utero activamente y que presentaron la lesión tan pronto ocurrió el primer contacto postnatal Sabemos que la reagina no atraviesa la placenta normal y por lo tanto una sensibilidad por la misma del tipo reaginico no es probable Cualquier otro anticuerpo podría pasar la barrera e igualmente los alimentos sensibilizantes como ocurre con la clara de huevo produciendo una sensibilización activa Hemos tenido casos en los cuales hemos podido hacer desaparecer las lesiones simplemente con suprimir de la dieta de la madre el alimento que se eliminaba por la leche

La dermatitis atopica no sigue siempre un curso progresivo vemos como incluso desaparece espontáneamente durante años o para siempre y solo quedan las manifestaciones respiratorias las cuales pueden incluso aparecer años después de la dermatitis

Hemos visto incluso casos en que la respuesta reagínica a una substancia ha desaparecido y en cambio ha aparecido otra Esto es de importancia senalar ya que no de bemos basar el diagnóstico en un estudio simple y pensar que cierto tiempo despues pueden ocurrir nuevas sensibilizaciones Además estas tienden en ocasiones a desaparecer después de cierto tiempo Es curioso que esto ocurra primero en casos en que la reacción clinica se produjo sin la aparición de reaginas Lo vemos en la infancia principalmente El suponer que haya un mecanismo distinto al reagínico no debe sin embargo llevarnos a desechar el estudio por medio de transferencias pasivas a estos enfermos Personalmente creo que me encontraría muy desorientado si no usare este método al cual me he acostumbrado durante tantos años Es muy superior a la prueba directa en la dermatitis —atópica cuya piel sabemos no reacciona normalmente por la enfermedad Además en muchas ocasiones el alergeno productor de la reagina es el mismo que causa el cuadro clinico y si aceptamos la otra hipótesis el alergeno tambien puede crear un anticuerpo celular aunque no tengan siempre que coincidir Además es el unico dato immunológico que podemos disponer para olvidarlo facil

mente En el futuro posiblmente será posible complementarlo con otro método que descubra la otra faceta del problema y permita llegar a un enjuiciamiento más completo

Se ha querido restar valor al prurito producido por la ingestion de alimentos al hecho de que las substancias proteicas vayan a acumularse a los sitios de inflamación

Sin negar que esto pueda ocurrir tenemos tantos casos en los cuales está claramente demostrada la causa del prurito, que éste debe ser considerado específico Es de recordar que los anticuerpos tienden a su vez a localizarse en los sitios de irritacion y esto de por si favorece las reacciones en los tejidos de shock Observando perfectamente a nuestro enfermo podemos diferenciar bien cuando un prurito ha sido producido especificamente y cuando no

Creemos que el diagnóstico etiológico de la dermatitis atópica debe ess a basado primeramente en un estudio detenido hecho por transferencias pasivas y por la discusión con el enfermo de la tolerancia a distintos alimentos y substancias diversas La presencia de reaginas nos ayudará a iniciar una comprobación de si esta coincide con la causa y si no para tenerlo en cuenta pues pudiere explicarnos más adelante una posible causa o simplemente la de otras manifestaciones asociadas Hemos visto muchas veces casos en los cuales hemos basado parte del tratamiento en la supresión de un alergeno por ejemplo el huevo y el enfermo ha seguido mal para encontrarnos despues de una revisión del caso de que el nino estaba tomando sopa de gallina o mantenido en contacto con una vivienda en la cual se usaba el huevo en cantid id

Yo he tenido la oportunidad de estudiar casos en los cuales immunologicamente pude comprobar la presencia del huevo en el polvo de la casa Fuera de estos casos positivos que todos conocemos hay muchos en los cuales no podemos encontrar relación entre los tests y la dermatitis Es en ellos donde debemos estudiar mejor aun nuestro enfermo por medio de dietas y comprobacion del contacto de cada alergeno so pechoso Muchas veces nos encontraremos gratificados por un hallazgo que hubiéramos desconocido por el hecho de ser los tests negativos Del estudio comparativo del tests pasivo y de las pruebas clinicas que hagamos con cada alergeno y del tipo de manifestación que éste produzca obtendremos con seguridad un gran apoyo para la terapéutica

Con frecuencia hay una sensibilización doble a alimentos y a inhalantes De ahi que para obtener un buen resultado hay que considerar ambos factores conjuntamente

El papel jugado por los inhalantes es de extrema importancia especialmente el polvo de casa y en menor grado el tabaco la caspa de animales los hongos ambientales etc etc Una hiposensibilización bien controlada y procurando no sobrepasar dosis que a veces son desencadenantes es de suma importancia Personalmente damos al papel del polvo un valor tan alto que a veces el exito de un cambio de lugar está en relacion con la disminución del contacto con este u otros inhalantes

El tramiento local es por supuesto de gran importancia Lo primero que debemos hacer es tratar la dermatitis segun la fase en que se encuentre con la medicación local apropiada y tratar de reducir las lesiones al minimo a evitar su contacto con el medio externo y disminuir la obstruccion de los conductos sudoríparos que se encuentran en ocasiones bloqueados Por

supuesto que el tranquilizar al enfermo y tratar de disminuir su excitabilidad y disminuir el prurito es de suma importancia El tratamiento depende por lo tanto del mayor numero de avenidas o factores que se tengan en cuenta y no pensar que toda la terapeutica de la dermatitis es el uso simplista de los corticoides que fuera de medicación antiinflamatoria y de restitucion no pueden tener ningun otro valor curativo Pueden servir para romper un círculo vicioso y para permitir iniciar un tratamiento con mejores resultados El tratamiento de la dermatitis atópica debe ser por tanto mixto por un lado suprimiendo disminuyendo o hiposensibilizando al enfermo y por otro reduciendo y llevando a la normalidad la piel

En la dermatitis atopica hay todavía algunas incógnitas a resolver lo que hace su estudio continue siendo muy apasionante La base de su mecanismo íntimo luce con todas probabilidades estar en relacion con las reacciones tisulares producidas por la interreacción entre antígenos y anticuerpos sin ya querer prejuzgar el tipo

Hemos querido hacer una revisión de los posibles mecanismos de produc ción de las lesiones de esta enfermedad exclusivamente desde el lado de la alergia lo contrario sería salirnos del marco de esta presentación Algunas de las explicaciones han tenido que ser por medio de hipótesis ya que de otra manera era practicamente imposible encontrar explicación a ciertos hechos La medicina está llena de hipótesis unas son transitorias y otras llegan finalmente a tener una comprobacion positiva Ambas tienen el merito de permitir explicar provisional o definitivamente una serie de hechos que de otra manera serían factores negativos y que impedirian el menor avance en el estudio de un problema que es lo que no debe ocurrir

RESUMEN

La dermatitis atopica debe considerarse como una manifestación alergica cutanea influenciada por factores secundarios y locales que pueden originar circulos viciosos que influyen en su evolucion

Como es un hecho comun la presencia de anticuerpos sensibilizantes de piel conjuntamente con eosinofilias sanguineas elevadas y la frecuencia de otras manifestaciones atópicas en el mismo enfermo y en sus antecedentes familiares hace que los factores inmunologicos deban ser considerados muy especialmente y no juzgados como simples coincidencias sin valor

Se ha hecho un estudio inmunologico detenido por medio de transferen cias pasivas pruebas de dilucion y neutralizacion busqueda de anticuerpos bloqueadores tests con retardantes y copulados pruebas de provocacion biopsias y estudio electroforetico de proteinas y lipidos sanguineos etc etc

Se estudia el mecanismo reaginico de las atopias en general y se enfoca en el caso particular de la dermatitis atopica senalandose las contradicciones derivadas de la falta de relacion entre algunos hallazgos inmunologicos y la no reproduccion o empeoramiento del cuadro clinico cuando se repetia el contacto alergenico La diferencia entre el habon urticariano y la lesion de dermatitis es considerada y el mecanismo de produccion de ambas es analizado

El estudio de la posibilidad de que otros mecanismos inmunologicos puedan estar actuando es enfocado muy especialmente el de las reacciones

tardias demoradas debidas a anticuerpos celulares que permiten explicar una serie de hechos contradictorios y muy especialmente la no produccion de las lesiones de dermatitis cuando se infecta intradermicamente el alergeno y su reproduccion en cambio en un buen numero de casos cuando el contacto se hace por otras vias

Se dedica igualmente atencion a los datos clinicos pruebas de provocacion vias de sensibilizacion alternancia de los sintomas y variaciones en la respuesta reaginica en estudios repetidos a intervalos de años en el mismo enfermo señalandose su importancia en las otras atopias asociadas como en la evolucion de la dermatitis misma

El mejor y mas apropiado tratamiento es el que se deriva de un minucioso estudio clinico del enfermo de sus dolencias y observaciones de los hallazgos *inmunologicos de los habitos alimenticios y contactos ambientales* de un claro conocimiento del mecanismo de produccion de la dermatitis de los factores desencadenantes de las alteraciones del mecanismo sudoral y de tantos otros factores asociados que actuan secundariamente De todo ese conjunto es que puede derivarse solamente un tratamiento alergico util y racional que combinado al tratamiento dermatologico dara los mejore frutos

RÉSUMÉ

L eczéma diathesique doit etre considéré comme une entite allergique cutanee bien qu il puisse etre influence par des facteurs locaux et secondaires créateurs de « cercles vicieux »

C est un fait communement admis que la présence simultanée d anticorps sensibilisateurs de la peau et d un degré éleve d eosinophilie ainsi que la frequence d autres manifestations observées chez un meme malade et dans ses antécedents familiaux doivent nous amener à accorder aux facteurs immunologiques une attention toute particuliere mais ceux ci peuvent etre egalement considéres comme des simples coincidences dépourvues de signification

Une etude immunologique est faite au moyen de transferts passifs tests de neutralisation et de titrage recherche des anticorps bloquants a ec des agents adjuvants et copulants tests provocateurs biopsies examen par électrophorese des proteines des lipides sanguins etc

Un examen critique de l ensemble est présenté ainsi que quelques considérations sur des faits observés et qui sont apparemment contradictoires

Sont séparement discutes et sous différents angles les mécanismes de l apparition de l eczema diathésique et des troubles respiratoires allergiques qui lui sont associés La difference existant entre les reactions de l *urticaire* et celles de l eczema sont étudiées

L importance possible de mecanismes immunologiques autres que les réactions réaginiques est etudiée principalement les reactions associées et differees qui pourraient etre dues à la production d anticorps cellulaires ce qui fournirait une explication des faits contradictoires observes

Les données cliniques les tests de provocation la connaissance de la voie de sensibilisation l alternance des symptomes et les différences de la reaction reaginique à quelques années d intervalle sont des éléments

permettant une meilleure étude des allergies respiratoires et de l eczema lui meme

Le meilleur traitement et celui dont on peut attendre le plus est celui qui resulte d un examen clinique approfondi des symptomes presentes par le malade des donnees immunologiques des habitudes alimentaires et des contacts du sujet avec le milieu ambiant d une connaissance nette du mecanisme provoquant l eczéma des facteurs declenchant la maladie *des troubles de la transpiration etc*

L ensemble de ces donnees permet d appliquer un traitement general et approprié de l etat d allergie qui pour donner de bons re ultats doit etre accompagne d une thérapeutique dermatologique sérieuse

SUMMARY

Atopic dermatitis must be considered as a cutaneous allergic entity although it can be influenced by secondary and local factors originating viscious circles

As it is a common finding the presence of skin sensitizing antibodies together with blood eosinophilia the role of hypersensitivity must be perfectly evaluated and not left apart by any reason. These findings should be considered as important facts favoring immunological mechanisms of production and not simple coincidences without real value

An immunological study is conducted by passive transfer sensitization neutralization and titration tests the study of blocking antibodies tests with copulating and adjuvant agents pro ocation te ts biopsies electrophoresis of blood proteins and lipids etc etc

A critic approach of the whole picture is presented together with considerations of some apparent contradictory facts observed The mechanisms of production of the atopic dermatitis and the associated respiratory allergies are separately discussed under different points of view The difference between the wheal and dermatitis reactions and their respective histological signification is considered

The possibility that other immunological mechanism besides the reaginic be of importance are studied mainly the associated delayed reactions by the possible production of cellular antibodies that permit to explain some of the contradictory facts

Clinical data and provocative tests route of sensitization alternation of symptoms and the variation in the reaginic response at several years intervals permits a better approach of the associated respiratory allergies and the dermatitis itself

The best and most promissing treatment of these cases is based on a careful clinical study and observation of the patient complaints in the immunological findings food habits and ambiental contacts and in the

therapy for a better result

ZUSAMMENFASSUNG

Die atopische Dermatitis muss dem Wesen nach als eine *Haut allergie* angesehen werden obwohl sie von sekundaren und lokalen Faktoren die einen Circulus vitiosus bilden konnen beeinflusst werden kann

Da gewohnlich Haut sensibilisierende Antikorper mit einer Bluteosinophilie zusammen gefunden werden muss dies fur die Rolle der Ueberempfindlichkeit genau studiert und nicht aus irgend einem Grunde beiseite geschoben werden Diese Erkenntnisse sollten als wichtige die immunologischen Produktionsmechanismen gunstig beeinflussenden Fakten angesehen werden und nicht als zufalliges Zusammentreffen ohne jeglicher Bedeutung

Eine immunologische Untersuchung wird durchgefuhrt mittels der passiven Uebertragungssensibilisierung Neutralisations — und Titulations — testen Tests mit blockierenden Antikorper mit bindenden und adjuvanten Agens Provokationstesten Biopsien der Elektrophorese von Blutproteinen und lipiden etc etc

Zusammen mit Betrachtungen uber einige beobachteten scheinbar kontradiktorischen Fakten wird eine kritische Zusammenstellung des Gesamtbildes gegeben Die Mechanismen zur Produktion einer atopischen Dermatitis und der respiratorischen Begleitallergien werden unter de verschiedensten Gesichtspunkten getrennt diskutiert Der Unterschied zwischen urtikarischen und Dermatitis Reaktionen und deren histologische Merkmale werden in Erwagung gezogen

Die Moglichkeit dass neben den Reagin Mechanismen noch andere Immunmechanismen von Bedeutung sein konnten wird studiert besonders der durch die mogliche Produktion zellularer Antikorper bedingten verzogerten Begleitreaktionen was die Erklarung mancher Kontradiktionsfakten erlaubt

Klinische Daten und Provokationsteste Wege der Sensibilisierung Wechsel der Symptome und die Variation der Reagin Antwort zu verschiedenen Jahresintervallen erlauben eine bessere Annaherung der respiratorischen Begleitallergien und der Dermatitis selbst

Die beste und am meisten versprechende Behandlung dieser Falle basiert auf einer sorgfaltigen klinischen Untersuchung und Beobachtung der Beschwerden des Patienten auf immunologische Erkenntnisse Ernahrungsgewohnheiten und Umweltskontakte sowie im Verstehen der der *Dermatitis produktion zugrundeliegenden* Mechanismen Hemnfaktoren Storungen des Schwitzens etc Wenn wir alle diese Aspekte zusammen fassen sind wir in der Lage eine geeignete Allergiebehandlung einzuleiten die immer zur Erzielung eines beseren Ergebnisses mit grundlicher dermatologischer Therapie kombiniert sein soll

QUELQUES ASPECTS DU CARACTÈRE HÉRÉDITAIRE DE L ECZÉMA DIATHÉSIQUE ET D AUTRES MALADIES « ATOPIQUES » (*)

par

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RÉSUMÉ

Ni l influence de l hérédite ni les relations genétiques existant entre certaines maladies atopiques (asthme bronchique rhinite allergique nevrodermite constitutionnelle ou eczéma diathésique) ne sont encore parfaitement connues

En premier lieu il faut nommer l hérédite dont l influence dominante n a pas encore ete completement determinée En nous basant sur une importante documentation personnelle il est permis d avancer ce qui suit

1 Les malades atteints de nevrodermites appartiennent a des familles ou se rencontrent deja l asthme et les rhinites avec ou sans manifestations de névrodermites

2 Les asthmatiques et les malades atteints de rhume des foins ne proviennent qu exceptionnellement de familles ou l on trouve des nevrodermites

3 Par contre les malades atteints d asthme ou de rhume des foins appartiennent a des familles ou se rencontrent des maladies atopiques respiratoires

4 La rhinite allergique a au point de vue de sa transmissibilite genetique une plus forte « penétration » que l asthme bronchique

5 La « penétration » génétique de l asthme bronchique est plus forte que celle de la nevrodermite constitutionnelle

La transmission par voie d heredité est fonction du milieu Les facteurs hereditaires creent pour certaines maladies atopiques un état de predisposition De ce fait les maladies atopiques peuvent etre considerees comme des maladies « idio dispositionnelles » héréditaires

L influence exercée par le milieu (péristase) se fait tres nettement sentir comme le montre le comportement de quelques jumeaux dont les cas ont été étudiés par nous Nous donnons quelques exemples

De ces observations il ressort que les maladies atopiques relevent de la pathologie familiale et que le milieu dans lequel elles se manifestent exerce une influence importante sur leurs caractéristiques

( ) Les Éd teurs regrettent vivement de ne pas avoir été en mesur de publier le rapport complet que l auteur a om s de leur fa e parven r l

SUMMARY

The influence of heredity and the genetic relations existing between certain atopic diseases (bronchial asthma allergic rhinitis constitutional neurodermatosis resp atopic d rmatitis) have not yet been fully inves tigated

We shall first name heredity whose predominant influence has not yet been completely determined

We shall make the following statements based on important and personally gathered evidence

1 Patients suffering from neurodermato is belong to families where asthma and rhinitis (with or without neurodermatic symptoms) can be found

2 Asthmatic or hay fever patients rarely belong to families in which cases of neurodermato is occur

3 On the other hand asthmatic or hay fever patients come from families where respiratory atopic diseases exist

4 Allergic rhinitis has from the point of view of its genetic transmissibility a greater power of « penetration » than bronchial asthma

5 Bronchial asthma has a stronger genetic « penetration » than consti tutional neurodermatosis

Hereditary factors bring about a condition of proneness to certain atopic diseases Hereditary transmissibility is influenced by the environment Therefore atopic diseases can be looked at as hereditary « idio disposi tional » diseases

The influence of the environment is very distinctly felt as our experi ments on the different behaviour of several twins will show

We give a few examples

From these observations it appears that the basis of atopic diseases is familial and that the environment in which they occur has an import nt influence on their type and features

ZUSAMMENFASSUNG

Weder der Erbgang noch die genetischen Beziehungen der atopischen Krankheiten untereinander (Asthma bronchiale Rhinitis allergica kons titutionelle Neurodermitis resp atopic dermatitis) sind restlos geklärt Im Vordergrund steht der unvollständig dominante Erbgang An Hand eines umfangreichen ei enen Materials kann gezeigt werden dass

1 Neurodermitiker in der Regel aus Familien mit asthmatischen rhinitischen oder und neurodermitischen Manifestationen stammen

2 Asthmatiker und Patienten mit Heuschnupfen nur ausnahmsweise einer Familie mit neurodermitischen Manifestationen angehören

3 Probanden mit Asthma oder Heuschnupfen hingegen aus Famil en mit Respirationsatopien stammen

4 Rhinitis allergica genetisch eine starkere Penetranz hat als Asthma bronchiale und

5 Asthma bronchiale genetisch penetranter ist als die konstitution lle Neurodermitis

Die Verschiedenheit der Penetranz durfte mit der unterschiedlichen Rolle der Umweltsfaktoren im Zusammenhang stehen Die Erbfaktoren praedisponieren lediglich zu gewissen atopischen Krankheiten Die Atopien gehoren somit zu den idiodispositionellen Erbkrankheiten Deutlich lasst sich der Einfluss der Umwelt (Peristase) am Verhalten eineiiger Zwillinge zeigen was mit Beispielen belegt wird

Daraus geht hervor dass die Atopien familienpathologisch weitgehend den fur die Sippe charakteristischen Ort der Krankheitsmanifestation bewahren

RESUMEN

Ni la influencia hereditaria ni las relaciones geneticas que existen entre ciertas enfermedades atopicas (asma bronquial rinitis alergica eczema diatésico) son bien conocidas En primer lugar es necesario señalar la herencia en la que la influencia dominante no ha sido completamente determinada En base a una importante documentación personal se llegan a las conclusiones siguientes

1 Los enfermos de neurodermitis pertenecen a familias donde se encuentran casos de asma y rinitis con o sin neurodermitis

2 Los asmaticos y polinicos pertenecen a familias donde la neurodermitis se encuentra excepcionalmente

3 Por el contrario en las familias de estos enfermos se encuentran enfermedades atopicas respiratorias

4 Desde el punto de vista de su transmision genética la rinitis alergica tiene una «penetración» mayor que el asma bronquial

5 La «penetración genetica del asma bronquial es mayor que la de la neurodermitis constitucional

La transmisión hereditaria es una función del medio ambiente Los factores hereditarios crean una predisposición Por lo tanto las enfermedades atópicas pueden ser consideradas como enfermedades hereditarias « idio disposicionales

La influencia del medio se hace sentir de manera neta como lo demuestra el comportamiento de los mellizos Se presentan algunos casos estudiados por el autor

Se concluye de todas estas observaciones que las enfermedades atopicas dependen de la patologiá familiar y que el medio ejerce una influencia importante sobre sus caracteristicas

LE TRAITEMENT LOCAL ET GÉNÉRAL DE L ECZÉMA DIATHÉSIQUE (DERMITE ATOPIQUE)

par

E SIDI A REINBERG et J BOURGEOIS SPINASSE

(Fondation A de Rothschild Service de dermato allergie Paris)

En nous fondant sur les essais thérapeutiques de ces cinq dernieres années dans notre service de la Fondation A de Rothschild nous voulons faire le point des resultats obtenus dans le traitement de l eczema diathesique compte tenu des acquisitions recentes dans le domaine des hormones corti costéroides Nous envisagerons successivement le traitement local et le trai tement general

LES CONSEILS HYGIÉNO DIÉTÉTIQUES

Le traitement doit etre precéde de toute une *prophylaxie* destinee à éli miner les facteurs aggravants car l allergène responsable n est que tres rare ment découvert.

On conseillera donc au malade

de se proteger de la *laine* et par prudence des poussieres des pollens des plumes de la soie en portant des vetements de lin ou de coton en recouvrant ses oreillers de housses en plastique en utilisant des matelas de caoutchouc mousse

d éviter tout contact avec les agents irritants le froid ou la chaleur exces sifs les produits de nettoyage savons detersifs on conseillera d utiliser des substituts du savon de prendre des bains rendus adoucissants par l amidon ou l huile de cade

On le mettra en garde contre les infections microbiennes ou virales contre les vaccinations surtout *antivariolique* et anticoquelucheuse et contre cer tains médicaments tels que la *penicilline*

Certains aliments sont a deconseiller les produits le plus souvent moins bien toleres sont lait œuf citron épinard poisson huile de foie de morue mais on déterminera le régime en fonction de l experience clinique et de l effet controlé de certaines dietes

Il faudra en outre tenir le plus grand compte du fait que certains sujets se trouvent mieux en atmosphere humide alors que d autres tirent profit

de climats chauds et secs Sans doute faut il voir la l effet de l humidité qui ramollissant la keratine libere les orifices sudoraux et favorise la sudation ou celui de la chaleur qui diminuant l œdeme péri orificiel attenue le prurit Mais l influence du climat n explique pas tout car ces malades hypersensibles aux allergenes existants dans leur milieu habituel se trouvent ameliores des qu ils s en éloignent C est ainsi qu une simple hospitalisation un changement de residence leur sont tres favorables jusqu au jour ou de nouvelles sensibilisations apparaissent dans le nouveau milieu Le phénomene on le voit est complexe et vaut qu on s y interesse

LE TRAITEMENT LOCAL

Il est dans tous les cas le principal « soutien » de la thérapeutique *Essentiellement symptomatique* il sera dicte par l aspect dermatologique de la dermite son stade evolutif son etendue la presence ou non de surinfection Toujours applique avec prudence apres une etude comparative de plusieurs produits sur des zones différentes de la peau atteinte il devra etre modifie au moindre signe d intolerance a la moindre sensation de chaleur de cuisson ou de prurit car chez un meme sujet telle medication locale bien toleree pendant quelques jours peut devenir irritante les jours suivants de meme que parfaitement supportée sur une région du corps elle peut provoquer des reactions sur une zone plus « sensible »

Dans les cas aigus suintants donc principalement dans l eczema du nourrisson on prescrira des pulvérisations ou des compresses d eau d Evian de serum physiologique ou de solution chloruree sulfatee et s il y a surinfection des compresses d eau permanganatee au 1/20 000 d héxomédine ou avec prudence pendant un temp tres court de neomycine Ces pansements humides seront renouvelés deux ou trois fois par jour et bientot alternés avec des lotions cremes ou pommades a l'hydrocortisone contenant ou non des antiseptiques ammonium quaternaire a do e infime G11 hexachlorofene oxyquinoleine rarement des antibiotiques On peut aussi appliquer les compresses humides sur une legere couche d axonge ou de creme à l hydrocortisone

L inflammation calmee c est le *prurit* qu il faudra soulager aussi complètement que possible A cet effet on évitera certains corps gras mal tolérés (huile d amandes douces) les colorants trop assechants dans ces eczemas non infectieux et rarement infectés et aussi les nombreuses pommades antiprurigineuses que l on utilisait avant la decouverte de l hydrocortisone Il est vrai que certains auteurs convaincus que les sensibilisations d origine externe sont rares chez les malades atopiques emploient encore couramment des pommades anesthésiques ou antihistaminiques souvent associées au phénol au camphre ou au menthol Nous pensons que le soulagement apporté par ces pommades est trop temporaire pour balancer la po sibilite des sensibilisations qu elles provoquent rarement il est vrai Et s il nous arrive — exceptionnellement car elles sont souvent irritantes — d utiliser des lotions mentholées et camphrées nous leur preferons les lo ions ou pommades à l oxyde de zinc les badigeonnages a l acide trichloracétique à 5 p 100 et surtout — nous y reviendrons — les pommades crem s et lotions à l hydrocortisone ou delta hydrocortisone

Lorsque la *lichenification* est importante le goudron de houille conserve son indication en tant que reducteur il assouplit la peau diminue la lichenification appliqué pur au pinceau ou sous forme de pommade a 5 ou 10 p 100 il donne le plus souvent de bons resultats On peut egalement recourir soit a l anthrarobine ou teinture d Arnings soit a des applications tres legeres d acide trichloracetique a 33 p 100 Tous ces traitements gagneront a etre pratiqués prudemment avec des pansements occlusifs car ceux ci peuvent meme a eux seuls sans autre medication locale se montrer tres efficaces Nous utilisons a cet effet des bandes adhesives élastiques hypoallergiques sans caoutchouc ni terpene Pour certains cas particulierement resistants ou la lesion est bien limitee il peut etre utile d avoir recours a la physiothérapie En raison de la chronicite de la dermite atopique la radiotherapie a éte abandonnee au profit de la buckytherapie qui est actuellement surtout dans certains pays etrangers un mode de traitement tres utilise et tres efficace pour des lesions localisees

Un traitement antiseborrhéique du cuir chevelu accompagnera toujours le traitement cutane Il comprend des applications de pommades au goudron decolore ou a l huile de cade alternes avec des lotions antiseborrhéiques et lorsqu il y a des lésions de grattage surinfectees des compresses d hexomedine et des cremes non grasses a l hydrocortisone avec antiseptique

La découverte de l *hydrocortisone* constitue en effet le plus grand progres realise depuis longtemps dans la therapeutique locale de l eczema Alors que les traitements locaux d acetate de cortisone s etaient revélés tres décevants tous les praticiens reconnaissent aujourd hui l efficacite des preparations d hydrocortisone Elles permettent d obtenir une sédation rapide du prurit un assouplissement progressif de la peau en general une amelioration remarquable Nous preferons souvent les utiliser a faible concentration de 0 5 a 1 p 100 dans un excipient gras s il est tolere

Mais a cote de ces resultats heureux la pratique a mis en evidence un certain nombre d inconvenients dont la frequence des recidives des l arret du traitement n est pas le moindre Comme l hydrocortisone par voie generale la pommade ne fait qu effacer les symptomes et les rechutes obligent dans ces eczémas chroniques a maintenir les lesions continuellement « sous controle » Or bien qu il y ait peu d accoutumance on constate qu a la longue l amelioration va s attenuant De plus la dessiccation que provoque cette médication en contre indique souvent l emploi sur ces epidermes presque ichtyosiques Enfin son inefficacite et meme le danger de son utilisation dans les dermites surinfectées ont conduit a lui associer des antibiotiques mais ceux ci possedent un tel pouvoir sensibilisant que nous preferons les antiseptiques indiques plus haut a la néomycine à la framycétine si couramment employees

C est encore pour tenter de remedier à ces inconvénients que nous avons expérimente diverses hormones corticoides preparees à des concentrations variables et surtout incorporees à des excipients differents

La lotion a l hydrocortisone nous a donne des resultats satisfaisants tant pour sa tolérance que pour son action tres voisine de celle de l hydrocortisone en pommade Elle est en plus d application facile sur de grandes étendues et ne nécessite aucun pansement Nous la trouvons cependant un peu desséchante

La pommade à la delta cortisone nous a paru le plus souvent moins efficace

sur le prurit comme sur les lesions cliniques Nos resultats inferieurs a ceux d Andrews coincident sur ce point avec ceux de Sulzberger et Rein. Il semble bien qu elle ne possede pas la meme constance d action que la pommade a l hydrocortisone et ne constitue pas par rapport a celle ci un progres notable

La pommade a la fluoro hydrocortisone s est montrée tres active lors des premieres applications plus active meme que l hydrocortisone puisque sa concentration est dix fois inferieure mais elle determine trop souvent au bout de 3 ou 4 jours des réactions érythemateuses et surtout œdemateuses qui font obstacle a son application sur de grandes surfaces comme à son emploi chez les enfants et les sujets presentant des retentions salines Waldbott et Fitzpatrick ont bien montre qu elle pouvait donner lieu a des modifications des electrolytes et de la protéinémie

D autres essais ont ete effectués avec les pommades a la *fluoro delta cortisone* ou a la *fluoro delta hydrocortisone* nous avons constaté une action remarquable parfois meme un peu supérieure a celle de l hydrocortisone (fluorodelta cortisone) mais a peu pres les memes inconvénients particulièrement l effet de dessiccation si regrettable pour le traitement des dermatoses *squameuses ou lichenifiees*

La pommade a la delta hydrocortisone dont la concentration utile est inferieure a celle de l hydrocortisone (0 5 % au lieu de 1 a 2 5 %) n a pas repondu aux espoirs que nous fondions sur elle

En revanche *le meme corticoide incorporé a des excipients semi fluides* moins gras plus penetrants nous a donné a la concentration de 0 1 % des résultats interessants parfaite tolérance action moins desséchante efficacite accrue facilité d application

C est que *la valeur d une preparation ne dépend pas seulement des qualites propres aux ingrédients actifs* mais aussi et pour une large part *de celles qui appartiennent a l excipient*

Nous portons donc toujours à celui ci une attention particuliere en étudiant sur un grand nombre de sujets son propre pouvoir d irritation et de sensibilisation

[illegible] les hormones corticoides constituent donc [illegible] ndition de choisir [illegible] llade et parmi les excipients, celui qu'indique l aspect dermatologique de la lésion

TRAITEMENT GÉNÉRAL

De multiples traitements ont éte proposés, mais aucun d entre eux ne donne de resultats satisfaisants dans tous les cas (31) aussi avons nous proposé d adapter une thérapeutique particuliere à chaque cas clinique

Traitement de désensibilisation spécifique

Alors que dans certaines manifestations allergiques telles que l asthme la rhinite spasmodique l urticaire la desensibilisation spécifique conduit à d excellents resultats les cas de dermite atopique ameliores par cette thérapeutique sont tres rares Pourtant les tests cutanés apres scarification

(Scratch test) ou après intradermo réaction sont relativement souvent positifs

Nous pensons cependant car on ne doit négliger aucune chance d ameliorer un malade que la désensibilisation specifique peut etre tentee chez les sujets dont les tests cutanés sont particulièrement positifs ou dont l histoire clinique est démonstrative (poussée évolutive au contact d un matelas de crin de cheval par exemple)

Les substances modifiant l activité nerveuse

Elles sont a conseiller dans la majorite des cas en raison de la frequence des troubles tels que l insomnie l irritabilite les dystonies neuro vegétatives

Ce sont encore les barbituriques associés ou non a la papavérine a la belladone [illegible] iren [illegible] sont partois extremement interessants (31) mais leur action est plus irréguliere leurs effets secondaires plus imprevisibles Il en est de meme des substances parasympathicommimetiques (manganochlorure d acetylcholine) dont l emploi a été preconisé par Aron Brunetiere (1)

Le choix d une substance modifiant l activite nerveuse est essentiellement fonde sur les réactions individuelles de chaque malade C est assez dire qu il faut « tâter sa susceptibilité » aux diverses drogues et qu aucune regle generale ne peut etre proposee

Le changement de milieu

C est une mesure therapeutique en genéral remarquablement efficace qu il s agisse d un changement de climat ou d un changement de milieu social (hospitalisation) Mais ici encore il n est pas possible de formuler une regle tel malade sera amelioré par la mer tel autre par la montagne etc Il est à noter que très souvent le malade connait par expérience le climat qui lui convient Dans la pratique des raisons economiques ou sociales viennent s opposer à la réalisation de ce changement salutaire de milieu

TRAITEMENTS HORMONAUX

A Traitement des dysendocrinies associées et particulièrement de la spasmophilie

L examen clinique d un malade souffrant de dermite atopique doit comporter la recherche de dysfonctionnement endocrinien que l on confirmera au besoin par des examens de laboratoire appropries

Le traitement de troubles post ménopausiques ou de dysménorrhée peut améliorer dans quelques cas une dermite atopique Encore faut il que le traitement hormonal vise à corriger un trouble objectif caractérisé par

que l exacerbation de la dermite se produise a un moment determine du cycle et que ses caracteres se conservent d un cycle au suivant Il est au contraire tres frequent d observer une certaine fantaisie des poussees menstruelles qui sont variables d un cycle à l autre survenant tantot en phase luteinique tantot en phase folliculinique disparaissant ou au contraire apparaissant avec le flux menstruel etc, chez une meme malade bien entendu

On a quelques chances d ameliorer les dermites bien rythmees par les regles par un traitement hormonal judicieusement adapté on risque de perdre son temps a vouloir tenter un traitement hormonal des poussées menstruelles a c racteres variables

La *spasmophilie* ou *tetanie chronique* semble une affection relativement plus fréquente chez les sujets souffrant de dermite atopique que dans une population de sujets non sélectionnés En France J Decourt (6) et H P Klotz (12 14) admettent que les spasmophilies représentent 7 a 8 p 100 de la population Les examens systématiques nous ont permis de denombrer 19 spasmophiles (13 femmes et 6 hommes) sur 130 cas de dermite atopique examinés soit 14 8 p 100

Le traitement instaure fut de la vitamine D2 ou du dihydrotachysterol associe ou non au calcium La symptomatologie et l évolution clinique de la spasmophilie commandaient seules la posologie et les resultats furent bons dans l ensemble La dermite atopique a disparu totalement chez 3 malades a éte très amelıorée chez 6 améliorée de manière satisfaisante chez 5 sujets chez 3 malades l effet a éte nul et 2 ont éte aggraves

Chez les 14 sujets ameliores dont 10 suivis depuis deux ans nous avons observe une évolution de meme sens de la dermite et de la spasmophilie

Le mode d action du traitement peut etre discute Rappelons seulement qu une baisse du calcium et du magnésium cutane a été signalee dans la dermite atopique (17) Le traitement calcique et la vitamine D₂ ont peu d effet chez les sujets non spasmophiles

Dans trois cas d *insuffisance thyroidienne* coexistant avec une dermite atopique nous avons observe un effet favorable de l opothérapie hormonale sur les deux affections Dans un cas d *hyperthyroidie* chez un malade souffrant de dermite atopique le traitement par le 4 methyl 2 thiouracile a e é suivi de l amélioration des deux affections

Il nous parait donc indiqué de rechercher et de traiter la spasmophilie et les dysthyroidies des malades souffrant de dermite atopique

B La corticothérapie

Elle permet de soulager un malade avec efficacité Ses avantages et ses inconvénients sont bien connus (31 37 29) aussi n aborderons nous que certains points qui méritent plus particulierement de retenir l attention

Quels sont les malades justiciables de cette thérapeutique ? En premier lieu ceux pour lesquels elle ne présente pas de danger Pour ce faire une enquete clinique sur le passe digestif mental etc de chaque malade est indispensable En second lieu elle doit etre reservée aux sujets les plus atteints soit par *l étendue,* soit par *l intensite* des lesions soit par le *caractere rebelle* des poussees evolutives tout en tenant compte de l âge du sexe et des occupations du malade

Quelle substance choisir? Il peut être utile à efficacité et doses équivalentes de faire des essais comparatifs des quatre principales substances delta cortisone delta hydrocortisone hydrocortisone (cortisol) et A C T H prises isolément ou en association

A quelles doses? les fortes doses (supérieures à 30 mg 24 h de delta cortisone) sont parfois utiles en début de traitement mais leur prescription comporte des risques et nécessite une surveillance clinique et biologique étroite Dans la pratique on peut le plus souvent proposer 15 mg d delta cortisone comme dose d attaque en essayant d réduire très progressivement — 1 mg par jour tous les 8 jours — jusqu aux doses d entretien de 10 mg ou 5 mg par jour

La durée du traitement sera déterminée par l évolution Il faut tenter de rendre l affection tolérable et non rechercher sa disparition complète Le traitement d une éventuelle affection associée peut permettre de réduire ou même de supprimer la corticothérapie c est pourquoi il faut systématiquement mettre à profit la rémission obtenue pour pousser les investigations cliniques et permettre un traitement éventuellement mieux adapté

Enfin les substances réputées cortico mimétiques (salicylate de soude acide acétyl salicylique etc) peuvent utilement remplacer ou relayer la corticothérapie

La découverte de nouveaux corticoïdes de synthèse pourrait peut être permettre d utiliser ces substances en évitant certains de leurs inconvénients et en leur conservant leurs avantages

TRAITEMENT PAR L HÉPARINE DE L HYPER BÉTA LIPOPROTÉINÉMIE DÉCOUVERTE DANS CERTAINS CAS DE DERMITE ATOPIQUE

Divers auteurs ont proposé de traiter les eczémas par l héparine (2 5 10) Nos résultats concernant les dermites atopiques restaient très inconstants jusqu à ce que nous ayons décidé de réserver ce traitement aux malades chez lesquels nous avions trouvé un taux sérique élevé des béta lipoprotéines

Parmi les examens biologiques pratiqués systématiquement chez nos malades figurait le test de floculation au phénol décrit par Kunkel (15) Sur 63 malades examinés en poussée évolutive de ce point de vue nous avons constaté que dans 15 cas la réaction de Kunkel au phénol était franchement augmentée Chez 26 malades examinés lors d une amélioration clinique la réaction de Kunkel au phénol n était perturbée que dans 3 cas Des examens complémentaires — identification par des techniques plus spécifiques entre autres réaction de Burstein au sulfate de dextrane (4) — confirmaient qu il s agissait bien dans nos cas d augmentation des béta lipoprotéines sans pour autant qu il s agisse de sujets hypertendus athéroscléreux ou présentant des modifications vasculaires du fond d œil (30)

L héparine administrée par voie per linguale à des doses quotidiennes variant de 20 à 50 mg pendant un à trois mois nous a permis d améliorer de façon remarquable 11 des 15 malades chez qui les béta lipoprotéines sériques avaient été trouvées élevées Deux des 4 malades non améliorés ont eu une réactivation de leur dermite après l héparine Nous conseillons aux femmes

soumises a ce traitement d observer une interruption au moment des règles car dans trois cas nous avons observe des metrorrhagies sans gravité d ailleurs

LE POUVOIR HISTAMINOPEXIQUE ET LE SÉRUM CAPTANT EFFICACEMENT L HISTAMINE

Le sérum sanguin de l adulte sain ou du malade non allergique peut capter *in vitro* une fraction de l histamine qui lui est ajoutee (J L Parrot, D A Urquia et C Laborde (16 20) Ce pouvoir histaminopexique est nul ou abaissé chez les sujets allergiques (21)

Nous avons evalue le pouvoir histaminopexique du sérum de 75 malades souffrant de dermite atopique en poussée évolutive et en dehors de tout traitement (23 28) Le pouvoir histaminopexique etait nul dans 57 cas abaisse à 10 p 100 dans 11 cas soit une perturbation survenant dans 9/10 des cas

Dans 46 cas de dermite atopique nous avons pu suivre les variations du pouvoir histaminopexique au cours des améliorations cliniques *dans 28 cas* sur 46 les valeurs serologiques se rapprochaient de la normale Nous avons constate que dans l ensemble les améliorations cliniques et l élévation du pouvoir *histaminopexique se développent simultanément sans qu il y ait* corrélation étroite entre le degré de l amélioration et la variation sérologique

Les améliorations cliniques de ces malades ont éte obtenues soit en traitant *une affection associée soit par des thérapeutiques non specifiques* soit par des injections de sérum humain captant hautement l histamine

Sous l influence d injection de serum humain (2 ml sous cutané) dont le *pouvoir histaminopexique était au moins de 30 p 100* diverses affections allergiques ont éte ameliorées (21 22) Dans l asthme notamment Bendi et Urquia (3) Parrot et Laborde (22) ont observé une amélioration chez 70 p 100 des sujets traités Nous avons applique cette therapeutique à 55 malades souffrant d dermite atopique et observe chez 19 d entre eux une amélioration indiscutable chez 2 d entre eux une réactivation sans gravite pas d effet net chez les autres Il semble donc que 1/3 des malades puissent tirer profit du serum captant l histamine L amélioration ainsi obtenue se manifeste de un a deux mois après la premiere injection de sérum, elle porte aussi bien sur l étendue que sur l intensite des lésions sa durée est variable de plusieurs mois à un an En cas de rechute une ou plusieurs injections de sérum peuvent determiner une nouvelle amélioration

La mesure du pouvoir histaminopexique apparait comme un moyen intéressant pour suivre l évolution d une dermite atopique *pour apprecier l efficacite* d une thérapeutique pour prevoir et prévenir une rechute éventuelle Le traitement par le sérum humain captant hautement l histamine mérite dans tous les cas d etre tenté *particulièrement s il existe* un pouvoir histaminopexique abaissé ou nul

RÉSUMÉ

Dans ce rapport il est question du résultat obtenu par le traitement local et général de l eczéma diathesique en tenant compte surtout des résultats obtenus par la corticothérapie

Apres les conseils hygiéno-diététiques qui ont leur importance est envisage le traitement symptomatique local suivant qu il s agisse de dermites aigues infectées ou lichenifiées etc

La corticotherapie locale a pris une place preponderante dans le traitement cutane Les differentes preparations des hormones corticoides ont donne des résultats variables suivant le constituant l excipient et l association utilisee

Quant au traitement general diverses modalites sont envisagees s adressant aux differents cas cliniques

— le traitement de desensibilisation spécifique ne donne que rarement de bons resultats

— les substances modifiant l activité nerveuse et les changements de milieu constituent un appoint therapeutique important dans presque tous les cas

Par contre le traitement du terrain n est a envisager que dans des cas détermines c est ainsi que sont étudiés les traitements des dysendocrinies associées et notamment de la spasmophilie des dysthyroidies

— la corticotherapie avec ses avantages certains mais ses inconvenients

— le traitement par l heparine avec de bons resultats lorsqu il existe une hyper beta lipoprotéinemie

— enfin l utilisation du sérum captant l histamine avec controle du pouvoir histaminopexique du sérum du malade

SUMMARY

Account is given here of the results of local and general treatment of atopic dermatitis chiefly of results gained by applying corticotherapy

After the hygieno dietetical advices which are important a treatment of local symptoms is considered according to the kind of the disease acute dermatitis infectious or lichenous forms

Corticotherapy is now the leading treatment for cutaneous cures There are differences in the various preparations of corticoid hormones and results have varied according to their excipient and components and in which way the compound has been made up

As regards general treatment various patterns are considered according to the different clinical cases

— specific de ensitization seldom gives good results

— substances active on the nervous system and changes of the patients ambiance are of powerful therapeutical aid for almost all cases

— on the contrary treatment of the terrain should only be employed in very specific cases therefore treatments of associated endocrine disturbances specially spasmophilia and diturbances of the thyroid are studied

— corticotherapy with its sure advantages and its drawbacks

The heparine treatment is successful in the case of existing hyper beta lipo proteinemia

Finally the use of histamino fixing serum with tests of the histamino pexic power of the patients serum are discussed

ZUSAMMENFASSUNG

In diesem Beitrag werden die Resultate der Lokal— und Allgemeinbehandlung des Diathese Ekzems besprochen besonderes Augenmerk wird auf die mittels der Corticotherapie erzielten Resultate gelegt

Nach einigen hygienisch diatetischen Ratschlagen die von Bedeutung sind wird die symptomatische Loaklbehandlung besp ochen je nachdem es sich um eine akute Dermatitis oder infizierte oder lichenifizierte Dermatitis handelt etc

In der Behandlung der Cutis hat die Corticotherapie einen sehr wichtigen Platz eingenommen Verschiedene Praparationen des kortikoiden Hormons [illegible] h dem Bestandteil dem Exzipienten

[illegible] ft so wurden bei verschieden n [illegible] ins Auge gefasst [illegible] gibt nur selten gute Ergebniss

— Die Nerventatigkeit modifizierende Stoffe und Milieuveranderungen bedeuten in fast allen Fällen ein wichtiges Therapeutikum

— Dagegen soll die Behandlung des Terrains nur in ganz bestimmten Fallen versucht werden so wurden die Behandlungen von kombinierten Dysendokrinien und namentlich der Spasmophilie und der Dysthyreoidien studiert

— Die Corticotherapie mit seinen gewissen Vorteilen aber auch s inen Nachteilen

— Die Heparinbehandlung mit guten Ergebnissen wenn eine Hyper Beta Proteinamie besteht

— Schliesslich die Verwendung von histaminentfernendem Serum unter Kontrolle der histaminopektischen Fahigkeit des Serum des Patienten

RESUMEN

Los autores se refieren a los resultados obtenidos por el tratamiento local y general del eczema diatésico en especial mediante la corticoterapia

Luego de los consejos higienico dietéticos que tienen su importancia, consideran el tratamiento sintomático local segun se trate de dermitis agudas infectadas liquenificadas etc La corticoterapia local ocupa un lugar predominante y los resultados son variables segun los constituyentes excipientes y asociaciones utilizados

En cuanto al tratamiento general se consideran diversas modalidades teniendo en cuenta los diversos casos clinicos

— la desensibilización especifica da muy raramente buenos resultatos

— lo cambios de ambiente y las sustancias que modifican la actividad

nerviosa constituyen un aporte terapeutico importante en casi todos los casos

Por el contrario los tratamientos del terreno constitucional están indicados sólo en casos determinados se consideran los tratamientos de las disendocrinias asociadas

— La corticoterapia tiene tambien sus inconvenientes

— El tratamiento con heparina da buenos resultados cuando existe hiper beta lipoproteinemia

— Finalmente el uso de sueros que captan la histamina con control de poder histaminopéxico del suero del paciente

SYMPOSIUM VII

L'allergie et son retentissement social dans les différents pays

Allergic management and problems in different parts of the world

Die Allergie und ihre soziale auswirkung in den Verschieden Landern.

Repercusiónes sociales de la afecciónes alérgicas en diferentes paises

NORWAY

by

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SUMMARY

In Norway as in other countries allergic diseases as a whole are very prevalent today and their frequency seems to grow constantly This impression may partly be due to the increasing interest in allergic diseases among practising physicians resulting in better diagnosis Such interpretation may especially be pertinent in the less distinct forms of the disease as e g when more or less obscure disturbances from the gastrointestinal tract prove to be allergic in their origin Asthma and hay fever however are so typical in their symptomatology that an increase in the registering of these diseases necessarily must mean a true augmentation of their frequency

Unfortunately there is no central institution in Norway showing an interest in this very important group of diseases consequently no statistics pertaining to the allergy frequency in the population are available More than twenty years of work with problems of allergy however have taught the author that allergic diseases are as frequent here as in other countries *It is therefore highly regrettable that no special institution for allergic diseases does exist not even in connection with the University clinics* The reason has not been lack of interest on the part of the medical profession on the contrary many physicians would in fact enthusiastically devote themselves entirely to this fascinating medical work In the circumstances however the physicians especially interested in allergy have been compelled to pursue their allergy studies rather as a hobby on their own time Everyone who has any knowledge of allergology will admit that this is highly unsatisfactory

There is some encouragement in the fact that since 1950 the medical students at the Oslo University have been given lectures on allergology

The most common allergic diseases in Norway are asthma hay fever eczema and urticaria The asthmatics represent a social problem of the first order It is of paramount importance to get these patients under treatment as early as possible trying to prevent the chronic asthma with its consequences Norway has a great number of asthmatic invalids

In the author s opinion most of the Norwegian asthmatics are bacterial allergics the exogenous asthmatics being in the minority In Norway hay fever is a surprisingly common disease spoiling for many people the short summer which is so very necessary in a country with a climate as severe as that of Norway The hay fever may be classed as follows a spring type (especially caused by pollen from birch), a summer type (pollen from grasses) and an autumn type caused by pollen from *artemisia vulgaris* (mugwort)

Eczema and urticaria do not differ notably from the same diseases in other countries

RÉSUMÉ

En Norvege comme dans les autres pays l ensemble des maladies allergiques joue un role important et la fréquence de leurs manifestations semble augmenter Cette impression est donnée au moins en partie par le fait que le diagnostic de ces maladies s affirmant les médecins portent un intéret croissant aux questions allergiques

Une semblable interprétation peut convenir plus particulièrement lors qu il s agit de gastro enterites et de troubles plus ou moins caractensés de l appareil gastro intestinal que l on peut en fin de compte attribuer à l allergie

Cependant l asthme et le rhume des foins presentent eux, des symptomes si nettement caractérisés que lorsqu une augmentation des cas signales se produit elle correspond bien en fait à une fréquence plus grande de la maladie

Malheureusement il n existe pas en Norvège d organisation centrale s occupant du groupe tres important de ces maladies et on ne dispose donc pas de statistiques permettant de connaitre exactement le nombre des cas et leur frequence

Au cours de vingt années consacrees a l etude des problèmes qu pose l allergie l auteur a cependant acquis la certitude de ce qu il y a autant de [illegible] Il est extre [illegible] ans les ques [illegible] tions d allergie en liaison avec les cliniques [illegible]

Ce n est guere parce que le corps médical ne témoigne pas d intéret pour l allergie bien au contraire il y a de nombreux médecins qui auraient le désir de pouvoir s adonner avec enthousiasme à ce travail médical passionnant Dans l etat actuel des choses les médecins qui s intéressent particulierement à l allergie ont dû poursuivre leurs études dans ce s ns en prenant sur leur temps de travail et un peu comme un « violon d Ingres »

Tous ceux qui savent ce qu est l allergologie seront obligés d admettre qu il s agit là d une situation particulierement peu satisfaisante Un certain encouragement nous vient cependant de ce que depuis 1950 l Université d Oslo a organisé des cours d allergologie

Les maladies allergiques les plus répandues en Norvège sont l asthme le rhume des foins l eczéma et l urticaire

Les asthmatiques posent un problème social de premiere importance Il y a un intéret primordial à pouvoir soigner ces malades aussitot que

possible pour prévenir l asthme chronique et ses consequences Il y a en Norvège beaucoup d asthmatiques pour lesquels la maladie revet le caractere d infirmite L auteur pense qu en Norvege la plupart des cas d asthme sont causés par l allergie microbienne les cas d asthme exogène représentant une minorité

En Norvege le rhume des foins est étonnamment frequent Il vient empecher beaucoup de gens de profiter du court eté dans un pays ou a cause de la dureté du climat le besoin d un bon ete se fait particulierement sentir

En Norvege on peut classer le rhume des foins en plusieurs types le rhume des foins de printemps (essentiellement du au pollen de bouleau) le rhume des foins d été (pollens de graminees) le rhume des foins d automne par le pollen de l *artemisia vulgaris* (mugwort)

En Norvege les problemes d eczemas ou d urticaires ne different sensiblement pas de ceux que l on rencontre dans les autres pays

ZUSAMMENFASSUNG

Allergische Erkrankungen sind heutzutage in Norwegen wie in den anderen Landeren sehr weit verbreitet und sie scheinen an Zahl standig zuzunehmen Dieser Eindruck konnte teilweise durch ein zunehmendes Interesse der praktischen Ärzte allergischen Erkrankungen gegenuber bedingt sein was eine bessere Diagnostik zur Folge hat Diese Vorstellung durfte besonders fur weniger bestimmte Formen dieser Erkrankung zuttreffen wie z B bei E G wenn mehr oder weniger deutliche Storungen von Seiten des Gastrointestinaltraktes sich in ihrem Ursprung als allergisch erweisen Asthma und Heufieber hingegen haben eine so typische Symptomatologie dass eine Zunahme der registrierten Falle dieser Erkrankungen mit einer wahren Frequenzvermehrung einhergehen muss

Ungluckhcherweise gibt es kein zentrales Amt in Norwegen das Interesse fur diese wichtige Krankheitsgruppe zeigt so dass folglich keine gultigen statistischen Daten uber die Allergiehaufigkeit in der Bevolkerung vorhanden sind Mehr als 20 Jahrige Arbeit uber Allergieprobleme lassen jedoch den Autoren die Meinung vertreten dass hier allergische Erkrankungen genau so haufig sind als in den anderen Landern *Es ist daher sehr bedauerlich dass keine spezielle Institution fur allergische Krankheiten besteht besonders nicht in Verbindung mit Universitatskliniken* Die Ursache hierfur lag nicht an mangelndem Interess der Ärzte im Gegenteil viele Ärzte wurden sich gerne dieser interessanten medizinischen Arbeit widmen Bei den herrschenden Umstanden jedoch waren die besonders an Allergie interessierten Ärzte gezwungen Allergiestudien als Hobby in ihrer Freizeit anzustlelen Jeder mit Allergologie vertraute Mensch wird bestatigen dass dies reichlich ungenugend ist

Es gibt aber eine gewisse Ermutigung da den Medizinstudenten an der Osloer Universitat seit 1950 Allergologie Vorlesungen gegeben wurden

Die am meisten verbreiteten allergischen Erkrankungen in Norwegen sind Asthma Heufieber Ekzem und Urticaria Die Asthmatiker stellen ein Sozialproblem ersten Grades dar Es ist von grosster Wichtigkeit diese Patienten so fruh wie moglich zu behandeln um so das chronische Asthma

mit seinen Folgen zu verhindern Norwegen hat viele Asthma Invaliden Nach der Auffassung des Autoren sind die meisten norwegischen Asthmafalle bakterielle Allergien die exogenen Asthmatiker sind in der Minderheit Heufieber ist in Norwegen eine uberraschend haufige Erkrankung die manchen Leuten den kurzen Sommer verderben, der in einem Lande mit einem so harten [illegible] Das Heufieber kann wie folgt [illegible] g Birkenbluten her [illegible] typ verursacht o [illegible]

Ekzem und Urticaria unterscheiden sich nicht von den gleichen Erkrankungen in anderen Landern

RESUMEN

En Noruega, como en otros países las enfermedades alergicas en conjunto son muy frecuentes en la actualidad y parecen aumentar constantemente Esto puede deberse en parte al mayor interés prestado por los médicos y por consiguiente a mejores diagnósticos Esto influye especialmente en las formas de difícil diagnóstico como por ejemplo ciertos trastornos gastrointestinales de origen alergico pero no en los casos de asma y polinosis típicos en su sintomatologia Por lo tanto debe concluirse que el aumento de casos refleja realmente una mayor incidencia de la enfermedad

Desgraciadamente no existe en Noruega ningun organismo central que se ocupe preferentemente de este grupo de enfermedades No hay por lo tanto estadísticas adecuadas El autor señala sin embargo su convicción, originada en 20 anos de especialidad de que los casos de alergia son tan frecuentes como en otros países Es lamentable que no haya ninguna institucion especializada ni siquiera en conexión con las clínicas universitarias Los médicos interesados en alergia deben realizar sus estudios por cuenta propia lo cual hace que los conocimientos adquiridos sean en general poco satisfactorios Un hecho alentador es que desde 1950 se dan clases sobre alergia a los estudiantes de medicina de la Universidad de Oslo

La enfermedad alergica mas frecuente en Noruega es el asma seguida de la polinosis el eczema y la urticaria El asmático representa un problema social de primera importancia pues es fundamental que los enfermos sean tratados lo antes posible para evitar la instalación del asma crónico Hay un elevado numero de inválidos asmáticos en Noruega En la mayoría de los casos se trata de asmas bacterianos siendo una minoría los causados por alergenos exógenos La polinosis es una enfermedad de una frecuencia excepcional en Noruega incapacitando a mucha gente en el corto verano tan necesario en un clima duro Hay tres tipos de polinosis de primavera causada en especial por el polen de abeto de verano (gramíneas) y de otoño (artemisia)

El eczema y la urticaria no difieren de manera importante de los tipos existentes en otros países

UNITED STATES

by

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ALLERGIC DISEASES

Incidence

In the United States of America with a population of 170 000 000 there are approximately 2 000 000 sufferers of bronchial asthma and 7 000 000 with hayfever Another 3 000 000 are afflicted with perennial allergic rhinitis urticaria atopic eczema dermatitis venenata drug allergy and collagen disorders Other less frequent allergic disorders such as migraine gastro intestinal genito urinary and central nervous system allergies would add to this number The incidence of major allergy is approximately 10 % of the population About 60 p 100 of the random population suffers from *all* forms of allergy when we include individuals with a history of minor episodic allergic manifestations

Asthma is of course the most debilitating and serious of all these afflictions In industry grain handlers bakers furriers laboratory workers farmers cabinet and wood working personnel as well as those exposed to strong chemicals and fumes are often victims of asthma as a result of their sensitivities at their occupations This condition causes a great economic loss Allergies are the *third* most prominent chronic disease in the United States following only heart disease and arthritis and rheumatism! The highest rates of asthma among occupational workers is 6 9 per 1 000 among men in agriculture 5 9 per 1 000 among professional men and 5 2 per 1 000 among business men

Hayfever and asthma account for 24 750 000 work days lost each year If one considers the occupational dermatoses the annual total loss in the United States including wages and cost of medical care is over $ 4 000 000 A recent survey showed an average period of disability of fifteen weeks per person with occupational dermatoses

Causes

Probably the most common cause of hayfever and asthma in the United States is ragweed pollen (The Ambrosia) This weed pollinates in the months of August and September The grass pollens are the next most common troublemakers The types of grasses which cause difficulty vary in species and in time of pollination in various sections of the country Timothy (Phleum pratense) Blue Grass (Poa pratensis) Orchard Grass (Dactylis glomerata) and Bermuda Grass (Capriola dactylon) are the most frequent allergens in this group The grass season extends from June through July in the Northeastern United States to almost perennial exposure in the Southwest and Far West

Pollen from trees of many species can cause difficulty but here again, the time of pollination and varieties of trees vary tremendously with the geography of the country

The most common fungi whose airborne spores produce allergies are *alternaria hormodendrum aspergillus* and *penicillium* Here again the type of mold spores present varies considerably in different parts of the country These spores are very infrequent in the desert and mountainous portions of our country but are very prevalent in the Great Plains of the Midwest and also the seashores In certain areas such as the region of the Great Lakes the Caddis Fly and the Mayfly are often very potent allergens causing seasonal symptoms In the Southwestern portion of our country seasonal symptoms are produced by an airborne allergen which has not as yet been determined This is called Factor X

Other insects such as ants butterfly moth, cricket and grasshopper have been suspected of producing allergic symptoms A committee of the American Academy of Allergy under the Chairmanship of Dr Frank Perlman has been actively investigating this problem Our President Dr S M Feinberg has also been doing a great deal of research along similar lines

Of course allergy reactions to the bites of insects such as wasp hornet bee and mosquito do occur in our country Even fatal reactions from this type of hypersensitivity have been reported

The United States is so large with marked differences in the climate and geography that one can not make too many generalizations Dr Max Samter has recently published a book called *Regional Allergy* covering these differences throughout our country

Undoubtedly the most common perennial allergen is house dust, closely followed in importance by feathers kapok cotton linters (mattress stuffing) and danders from such animals as cats dogs parakeets and horses The dust factor is more prevalent in the colder climates where central heating systems are required and where more furniture and rugs are present in the homes

Unfortunately the active principle of the house dust allergen has not as yet, been determined Some workers feel that bacteria or their products or mold spores play a major role in dust allergy but this matter needs further study

Foods as a primary cause of asthma and rhinitis are not nearly as common etiologic agents as are the inhalants particularly in adults In children

with infantile or atopic eczema and in some cases of asthma and allergic rhinitis they do play a more important role They are frequently secondary allergens in both children and adults In my opinion a few enthusiastic investigators in our country stress food sensitivities far beyond their true importance Of course minor allergy to foods has been shown to aggravate the symptoms of a patient with pollenosis when ingested at that time of year The foods most likely to cause difficulty are milk wheat eggs nuts fish and seeds (such as mustard and flax)

Of the contactants the oleoresins of poison ivy poison oak and sumac are the most troublesome seasonal allergens in causing dermititis In industry the various cutting oils are very prominent offenders In the home soaps detergents and cleaning solutions are often the cause of contact dermititis

Bronchial asthma can be caused by any of the above foods inhalants and seasonal factors It may very often be aggravated by super imposed respiratory infections The chief organisms usually involved are the various gram positive organisms as the streptococcus and staphylococcus Hemo philus Influenza B Coli and B Aerogenes are also frequently seen in sputum cultures and bronchoscopic washings We have no indisputable proof however that the patient is allergically sensitive to them or that they are causally related to the asthma

There are also those asthmatics who have no evidence of extrinsic allergies but have infections either in their sinuses and tracheo bronchial tree For lack of a better term this type of asthma is usually called intrinsic asthma These are usually patients whose symptoms come on in the fourth or fifth decade of life and they may or may not have a family history of allergy They usually have a blood eosinophilia over 10 p 100 There are also some children who fall in this category

Allergy to drugs is very common in the United States The promiscuous use of penicillin has produced many allergic reactions—frequently fatal Acetyl salicylic acid is also a relatively common cause of asthma and is usually associated with intractable wheezing pansinusitis and nasal poly posis

Diagnosis

Skin tests are used only after a very thorough history and physical exa mination has been done to rule out any other conditions which may simu late an allergic disorder These surveys would also include the essential laboratory procedures such as X rays cardiograms blood counts and sputum studies Respiratory function tests before and after broncho dilators bronchoscopy nasal and bronchial secretions for eosinophils and micro organisms are often necessary for a complete workup and diagnosis

The importance of the results of skin tests must not be over emphasized It is merely one of the many procedures used to determine the etiologic factors involved One must realize the pitfalls of non specific irritating reactions as well as the negative reactions because of poor allergens used or lack of responsiveness of an abnormal skin In order to be really sure of the significance of positive skin tests clinical exposures to these subs tances must be carried out Therefore skin tests are of importance

depending upon (1) who does the tests and interprets the reactions ( ) how they are performed and (3) what materials are used as allergens

One of the most frequent criticisms we as allergists receive from our fellow physicians is that we find our patients allergic to *everything*

Except along the Atlantic Seaboard in such centers as Boston New York Baltimore Philadelphia and Buffalo it is the practise in most places in the United States to do preliminary scratch or prick tests as a screening procedure prior to performing intradermal skin tests The scratch or prick technique is less hazardous but not nearly as sensitive as the intradermal technique It also gives fewer positive reactions

The technique of the scratch test consists of making from ten to fifteen scratches on the back or arm and then applying a minute amount of either the moistened powdered extract or the concentrated (glycerinated usually) extract of the test substance A small instrument capable of excoriating the skin without drawing any blood is used

The intracutaneous test is performed by introducing a minute amount (1/50 to 1/100 cc) of a highly diluted saline extract of the allergen intradermally with a tuberculin syringe and a #26 or #27 gauge short beveled needle

The usual testing dilutions for intradermal skin tests vary from 1 10 to 1 10 000 depending upon the antigen used Fruits and vegetables are tested in dilutions of 1 10 whereas the seeds such as mustard flaxseed and cottonseed pollens fungi and other potent allergens may be first tested with dilutions of 1 10 000 or higher This would depend on the clinical history which is first obtained Naturally a strong clinical history of a suspected allergen must be tested in very high dilutions and with extreme caution Preliminary scratch tests on these instances are preferable Recently I reported a case of a man who gave a marked reaction to an intradermal skin test with mouse serum in a dilution of 1 to 1 *billion*

A marked or 4 plus reaction usually has a large wheal with pseudopods and a surrounding large area of erythema A moderate or 3 plus reaction would not have pseudopods but would have a large wheal and erythema A slight or 2 plus reaction would appear as a smaller degree of wheal and less erythema

A careful history is taken then intradermal tests with high dilutions of antigen or preliminary screening with scratch tests are done before more concentrated extracts are used These tests can be dangerous unless these precautions are taken

Extracts of pollen and fungi are usually made up as 3 p 100 to 5 p 100 weight to volume of the defatted material in a buffered saline solution Some laboratories make up their extracts in 50 p 100 glycerin since these are more stable than the saline extracts Saline extracts lose considerable potency even if stored in the ice box for one year hence in hyposensitization therapy the dosage should be cut to one half the amount of the older extract when a fresh extract is used A few clinics in the United States make up their pollen antigens in gelatin for therapeutic injection This apparently slows the absorption of the extract and tends to prevent immediate constitutional reactions Gelatin solutions can not be used for skin testing

Unfortunately there is no generally accepted method of standardizing

of extracts There are three chief methods used in the United States Namely the weight to volume the total nitrogen basis and the protein nitrogen basis (Phosphotungistic acid precipitable N as described by Doctor Cooke and his co workers) Roughly a 5 p 100 extract of timothy pollen is equivalent to about 40 000 protein nitrogen units per cc or 8 mg total nitrogen/cc

Food extracts of juicy fruits and vegetables are prepared by extracting the juice from these materials and diluting this with an equal volume of buffered saline solution The extracts are then passed through a Berkfeld or Seitz filter bottled sterily and then frozen in small aliquots until ready for use

We do not consider delayed skin reactions to the various allergens of pollens epidermals inhalants or food of clinical significance However the tuberculin and other bacterial antigens are not included in this view

Usually only selected tests are done when one wishes to coordinate a history of exposure to certain environmental or seasonal factors This might include anywhere from twenty to forty tests However in many instances the physician can not get any clues or leads from the history and then as many as one hundred and fifty to two hundred skin tests may have to be performed Testing with food extracts as you all know leaves much to be desired A positive test does not necessarily indicate clinical sensitivity and a negative test does not always mean that this food is not the culprit Also fresh fruit and vegetable extracts tend to deteriorate very rapidly and several of the foods such as pepper white potato and carrots can often produce non specific positive reactions

The best method for determining allergy to foods is by elimination or trial diets There are two favorite methods of approach to this problem The first is to place the patient on a diet composed of four or five basic foods such as rice lamb grapefruit and pears for a period of five to six days Then if the patient becomes symptom free one food is added every two to three days to the basic diet noting those foods which induce symptoms The second method of food trials is to allow all foods with the exception of basic foods such as milk wheat and eggs or all cereal grains for a period of two weeks (Rowe diets) If the patient becomes symptom free the foods which were originally omitted are added one at a time and the effects noted If this elimination diet does not work out other foods may be omitted such as fruits and vegetables meats and/or fish and again the same procedure instituted

Food diaries in our hands are most difficult to evaluate particularly in a patient with a chronic disorder Also most patients do not follow the instructions and neglect to record everything ingested such as milk in coffee or pepper on food or drugs such as aspirin or cathartics However if an intelligent patient is subject only to intermittent attacks of allergic symptoms the food diary can often be of much assistance in identifying those foods which produce the symptoms

Other diagnostic tests are the mucous membrane tests These are employed in those patients who give a clinical history of symptoms during a particular pollen or fungus season yet show negative intradermal skin tests even in high concentrations A small amount of powdered allergen can be placed in the conj

demonstrates a positive reaction therefore a presumed sensitivity to the tested allergen

This same powdered allergen may be placed in the nose with a swab or [illegible]

Some investigators in our country have used bronchial inhalation tests. These can be very hazardous and are not recommended except for carefully controlled experimental studies

In those patients who have a generalized skin eruption which prohibits direct skin tests or who live far away from the physician or in small infants passive transfer (Prausnitz Kuestner) tests are often employed Of course one must make sure that the patient has a negative serology, and no past history of hepatitis or malaria The recipient must be known not to have any positive skin tests or history of allergy and should be warned not to eat any of the foods which are suspected from the clinical history The Leucopenic Index and the non reaginic allergy pulse tests are not generally used or accepted by most allergists in the United States

At the present time very few allergists in the United States test with bacterial extracts or vaccines Years ago this was common practise but one could never determine the significance of either the immediate or delayed type of reaction There is one exception however Occasionally a patient on repeated sputum or sinus cultures will be infected with the same organism Positive reactions to a vaccine prepared from this organism would be significant

Therapy

Hyposensitization (desensitization) certainly is used in the treatment of seasonal or perennial allergic rhinitis and bronchial asthma The chief allergens used in treatment are the pollens of ragweed grasses and trees the common airborne fungi such as alternaria and hormodendrum the usual inhalants such as house dust kapok animal danders feathers and certain airborne insects

Desensitization by injection with foods is never used, and with certain drugs as penicillin extremely rare However injections with the inhalants and pollens and fungi are also given in lesser dosage schedules for the treatment of atopic eczema but are not used in cases of chronic urticaria. Injections with dander extracts is only rarely employed except when the patient by reason of his occupation such as a laboratory worker veterinarian, farmer or horse jockey can not avoid his offending factors

Treatments are given subcutaneously usually once or twice weekly The initial dose is usually 1/10 cc of the dilution of extract which give a slight reaction by intracutaneous skin tests These dosages are increased as regularly as the patient can tolerate without producing marked local or systemic reactions During the pollen seasons the dosage attained prior to the season is usually cut back two to three doses Once the maximum optimal dosage is attained this same dosage is repeated once every three to five weeks on a perennial basis Unfortunately we have no true

method of identifying the patient who will do well after discontinuing hyposensitization injections In our experience about 50 p 100 of patients who do stop treatment after three years without symptoms find that they have a recurrence of their symptoms the very next pollen season Of the remaining patients some may never need further therapy but the greatest majority have a recurrence within five years after stopping the injections

ALLERGY SOCIETIES AND EDUCATION IN ALLERGY IN THE UNITED STATES

There are two national allergy societies in the United States The American Academy of Allergy and the American College of Allergists The Academy of Allergy was formed by the union of the fi st two original allergy societies in America namely the Society for the Study of Asthma and Allied Conditions and the Society for the Study of Allergy These organizations were formed in 1923 The American College of Allergy was formed in 1943 There are over one thousand members and fellows in each of the two national societies However many allergists belong to both societies There are over fifteen hundred physicians who do allergy either full time or part time Of these approximately one third or five hundred devote all of almost all of their time to the practice study and investigation of allergy There are approximately 120 000 physicians in the active practise of medicine in the United States Those practising allergy therefore constitute about 1 p 100 of all active practitioners

Hence one can see that all allergy problems can not be treated by the allergists alone There would be about 10 000 patients for each specialist Therefore the non specialist in allergy must be made capable to handle the majority of allergy problems including acute manifestations drug allergies and the less complicated persistent conditions Unfortunately physicians who graduated twenty five years ago or earlier had little or no instruction in allergy In order to correct this deficiency intensive postgraduate courses are given from time to time by various medical schools the national societies of allergy and the American College of Physicians Sections on allergy in many of the state medical societies and the American Medical Association present programs of interest and instruction to the general medical profession There are also many state and local and regional allergy societies in the United States which conduct frequent scientific meetings

Medical students are exposed to allergy training in various degrees in the different medical schools of the country A few schools give as many as twelve to fifteen lectures on allergy plus 20 to 30 hours in the allergy clinics In addition to this lectures in immunology on the fundamentals of anaphylaxis hypersensitiveness and serum disease are also given A few schools have no formal lectures or attendance in approved allergy clinics Here the students obtain their experience in the broad parent specialties of internal medicine and pediatrics in the wards and out patient departments of teaching hospitals However these schools are few and far between and more and more attention and time is being given to the specialty of allergy

In order to become a recognized specialist in allergy in the United States

the physician must first fulfill the specific requirements of training in either internal medicine or pediatrics This takes three to four years after graduation Then one to two years of the study of allergy in a recognized center is necessary There are about thirty institutions in the United States that have approved training programs in allergy Written and oral examinations must be completed successfully in the parent speciality of medicine or pediatrics and also in allergy If the student passes these examinations successfully he is then certified as a specialist in allergy There have been only 270 to 300 physicians so certified to date

The public knowledge and interest in allergy has been greatly increased in the past five years through the efforts of the Allergy Foundation of America This organization has as one of its main functions the education of the public about allergy This is conducted by means of booklets on hayfever asthma and childhood allergy by radio and television announcements and programs about allergy and by a general information service

Another indication that allergy is well thought of in this country is the recent formation by the United States Government of the National Institute of Allergy and Infectious Diseases This institute a part of the National Institutes of Health of the U S Public Health Service does fundamental research in allergy and also distributes funds to individual investigators for their own research In the past two years more money has been available for research in allergy and related fields than ever before If a research worker or clinician has a good project for study and applies f ... budget

I

vided the United States Budget has provided sufficient financial supp... this Institute

SUMMARY

Approximately ten percent (10 p 100) of the population in the United States has some major form of allergy such as asthma allergic rhinitis, or urticaria Allergies are the third most common chronic disease in our country This produces a great economic loss as 24 750 000 work days are lost each year because of just allergic rhinitis and asthma

The chief seasonal airborne allergens which cause the most difficulty vary greatly because of differences in the geography and climate Probably the greatest single offender is ragweed pollen (Ambrosia) closely followed by grass pollens tree pollens and fungi The primary mold allergens are alternaria and hormodendrum

Undoubtedly house dust is the most common perennial allergen but animal danders and cotton fibers may play an important role Foods as a primary cause of respiratory allergy particularly in adults are not nearly as common as inhalants and/or infection As is so well known, many asthmatics have no demonstrable extrinsic allergies but have infections either in their sinuses and/or tracheobronchial tree These asthmatics

are called intrinsic and are associated with a blood eosinophilia over ten percent (10 p 100) and the symptoms usually develop over forty years of age The most common drug allergies we encounter are those from penicillin and acetyl salicylic acid

DIAGNOSIS A complete allergic survey entails a thorough history and physical examination X rays of chest and sinuses electrocardiograms blood counts nasal and sputum studies and respiratory function tests Skin tests are of value but must not be over emphasized as false negative and positive reactions do occur It is the usual practise in the United States to first do preliminary screening tests by the scratch test method and then follow with intradermal testing when indicated In certain sections of our country only intradermal tests are utilized but this technique can be very hazardous unless a careful history is first performed and the physician is very familiar with his allergens and his patient

Extracts of pollens and fungi used for testing and hyposensitization therapy are usually 3 p 100 to 5 p 100 extracts of the defatted material in either buffered saline or glycerosaline solutions

Skin tests with food extracts leave much to be desired The best methods of determining allergies to foods are by various elimination or trial diets Testing with bacterial antigens and vaccines has practically been discarded in our country

SPECIFIC THERAPY Hyposensitization (desensitization) with inhalants pollens and fungi are used very frequently in the treatment of allergic rhinitis and bronchial asthma and to a lesser intent in atopic eczema Hyposensitization for food allergies is never employed

ALLERGY SOCIETIES AND EDUCATION IN THE UNITED STATES The two major national societies of allergy in the United States are the American Academy of Allergy and the American College of Allergists There are approximately twelve hundred (1200) members in each group but there are dual memberships There are about fifteen hundred (1500) physicians who specialize in allergy which constitues about one per cent (1 p 100) of all active practitioners

In order to become a recognized specialist in allergy in the United States one must spend one to two years for the study of allergy in a recognized center after complete previous training in either internal medicine or pediatrics There are about thirty (30) institutions in the United States which have approved training programs in allergy There are only about three hundred (300) physicians who have qualified with this type of training

The Allergy Foundation of America has as its primary function education of the public about allergy This is conducted by means of booklets on hayfever asthma and childhood allergy by radio and television announcements and programs on allergy

The National Institute of Allergy and Infectious Diseases does fundamental research in the field of allergy and also allocates funds to individuals for their own research problems Since the establishment of this institute more money as been made available for research in allergy and allied fields han ever before

RÉSUMÉ

Environ 10 p 100 de la population des États Unis souffrent de quelque forme d allergie caractérisée telle que l asthme la rhinite allergique ou l urticaire Les maladies allergiques arrivent au troisieme rang des maladies chroniques courantes aux États Unis Elles causent a l economie un preju dice important du fait que la perte annuelle de 24 750 000 journees de travail est imputable à l asthme et à la rhinite allergique

Les principaux agents allergenes saisonniers sont ceux qui causent le plus de difficultés étant donné qu ils sont differents selon les climats et les contrées Le principal agent allergénique est le « Ragweed » ou Ambrosia que suivent de pres les pollens de graminees, les pollens des arbres et les moisissures Les principaux allergenes fongiques sont l Alternaria et l'Hor modendron

La poussiere domestique est sans doute l allergene le plus fréquent et le plus constant mais les squames des animaux et les fibres de coton jouent aussi un role important Les aliments sont, surtout chez les adultes, une cause principale de troubles allergiques respiratoires mais plus rare que les substances inhalées ou que l infection

Il est bien connu que beaucoup d asthmatiques ne presentent pas de symptomes d allergie extrinseque que l on puisse identifier mais par contre ils ont des infections de leurs sinus de leur trachee ou de leurs bronches Ces asthmatiques sont désignés comme des cas d asthme « intrinseque » chez eux les manifestations de la maladie s accompagnent d une éosino philie sanguine dépassant 10 p 100 et ces symptomes font généralemen leur apparition apres la quarantaine Les allergies medicamenteuses que nous rencontrons le plus souvent sont dues à la penicilline et à l acide acétyl salicylique

DIAGNOSTIC Un examen allergologique complet suppose une connais sance parfaite de l histoire de la maladie et de l état physique du sujet examen aux rayons X de l appareil respiratoire et des sinus electro-cardio gramme numeration globulaire étude des sécretions rhino pharyngées et bronchiques et des tests de la fonction respiratoire

Les tests cutanés ont une valeur qui ne doit pas e re surestimée et de fausses réactions positives ou négatives se produisent parfois

Il est de pratique courante aux États Unis de procéder d abord à des tests éliminatoires par la methode des cuti réactions puis par des essais intradermiques s il y a lieu Dans certaines contrees de notre pays seuls les tests intradermiques sont pratiques ce qui comporte des risques sérieux quand le médecin traitant n a pas préalablement pris grand soin de connaitre l historique medical du sujet et qu il n est pas tres familiarisé avec les al[illegible] genes et son patient

Les extraits de pollens et de moisissures utilisés pour les tests et pour les traitements de désensibilisation sont généralement des extraits titrés à 3 p 100 et 5 p 100 tirés des substances dégraissées presentées sous la forme de solutions tampons salines ou de solutions glycérosalines

Les tests cutanés faits avec des extraits d aliments laissent beaucoup à desirer La meilleure methode pour déterminer l allergie alimentaire con

siste à *procéder par élimination avec des régimes alimentaires d essai* *On a* pratiquement renoncé dans notre pays aux tests faits au moyen de vaccins et d antigenes bactériens

TRAITEMENT SPECIFIQUE la desensibilisation aux pneumallergenes tels que pollens moisissures et poussière est tres fréquemment pratiquee dans le traitement de la rhinite allergique de l asthme allergique et moins souvent pour l eczéma diathésique La desensibilisation aux allergènes alimentaires n est jamais employée

SOCIETÉ D ALLERGOLOGIE ET ENSEIGNEMENT ALLERGOLOGIQUE AUX U S A les deux principales societes d allergologie des États Unis sont « l American Academy of Allergy » et « l American College of Allergists » Chacune de ces sociétes compte 1 200 membres mais certains de leurs adherents sont à la fois membres des deux sociétes

Il y a environ 1 500 médecins spécialisés dans l allergologie ce qui repré sente environ 1 p 100 du total des praticiens exerçant aux U S A

Pour etre reconnu comme specialiste dans l allergologie aux États Unis un stage d études de 1 à 2 ans dans un centre d instruction agréé est exigible auparavant le médecin doit avoir termine ses études de médecine et avoir un certificat de médecine interne ou de pédiatrie Il y a aux États Unis environ 30 Centres d Études ou est enseigné un programme d allergologie *officiellement approuvé Il n y a guère que 300 médecins ayant fait* ces etudes spéciales La tache principale de l « Allergy Foundation of America » est l éducation du public il y est procedé par voie de brochures sur l asthme le rhume des foins et l allergie infantile et aussi par des programmes radio diffuses et télévises

Le « National Institute of Allergy and Infectious Diseases » entreprend des recherches sur les problemes fondamentaux du domaine allergologique elle accorde aussi une aide financière aux chercheurs qui se consacrent a des études personnelles Depuis la fondation de cet Institut la recherche scien tifique en matiere d allergologie a vu mettre à sa disposition plus de moyens financiers qu elle n en avait jamais eus

ZUSAMMENFASSUNG

Annahernd zehn Prozent (10 p 100) der Bevolkerung in den Vereinigten Staaten haben irgendeine schwerere Form von Allergie wie Asthma allergische Rhinitis oder Urticaria Allergien sind die dritthaufigste chro nische Erkrankung in unserem Lande Dies erzeugt einen grossen volks wirtschaftlichen Verlust 24 750 000 Werktage gehen jedes Jahr schon allein wegen allergischer Rhinitis und Asthma verloren

Die hauptsachlichen und grossten Schwierigkeiten hervorrufenden wahrend bestimmter Jahreszeiten durch die Luft ubertragenen Allergene variieren stark wegen der geographischen und klimatischen Unterschiede Wahrscheinlich ist das wichtigste unter innen das Ragweed (Ambrosia) dicht gefolgt von Graspollen Blutenstaub von Baumen und Pilzen Die erstmals dargestellten *Allergene sind Alternaria und Hormodendrum*

Zweifellos ist der hausliche Staub das am meisten verb[illegible]

lich einwirkende Allergen doch konnen auch Substanzen tierischer Natur und Baumwollfasern eine wichtige Rolle spielen Nahrungsmittel als der primare Grund einer Allergie des Respirationstraktes besonders bei Erwachsenen sind nicht annahernd so haufig als inhalierte Stoffe und/oder Infektionen Bekanntlich haben viele Asthmatiker keine aufzeigbaren ausserlichen Allergien wohl aber Infektionen in ihren Sinus und/oder Tracheobronchealbaum Diese Asthmatiker werden innerliche (intrinsic) genannt haben zugleich eine Bluteosinophilie uber zehn Prozent (10 p 100) und die Symptome treten gewohnlich erst nach dem 40 Lebensjahre auf Die verbreitetsten Arzneimittelallergien die wir kennen, sind die des Penicillins und der Acetylsalicylsaure

Diagnose Eine komplete Untersuchung auf Allergien erfordert eine profunde Anamnese und physischen Status Rontgenaufnahmen des Thorax und der Sinus Elektrokardiogramm Blutstatus Naxen und Sputumexamen und Respirationsfunktionsteste Hautteste sind wertvoll, sollen aber nicht uberschatzt werden da falsche negative und positive Reaktionen vorkommen konnen Es ist in den Vereignten Staaten ublich erste Auslesetests mittels einer Skarifikationsmethode anzustellen und dann wenn angezeigt Intradermalteste volgen zu lassen In einigen Teilen unseres Landes werden nur Intradermalteste angewandt aber diese Technik kann sehr gefahrlich sein wenn man nicht vorher seine sorgfaltige Anamnese aufstellt und der Arzt nicht sehr vertraut mit seinen Allergenen und dem Patienten ist

Die fur Tests und Hyposensibilisationstherapie verwendeten Extrakte von Pollen und Pilzen sind gewohnlich 3 p 100 bis 5 p 100 ige Extrakte des entfetteten Materials entweder in gepufferten Salz oder Glycero-Salz losungen

Hautteste mit Lebensmittelextrakten lassen viel zu wunschen ubrig Die besten Methoden Allergien gegenuber Lebensmittel aufzudecken fussen auf wechselnder Elimination und Probediat Teste mit Bakterienantigenen und Vaccinen wurden in unserem Lande praktisch wieder verlassen

Spezifische Therapie Hyposensibilisierung (Desensibilisierung) durch Injektionen von Pollen und Pilzen Extrakten wird in der Behandlung der allergischen Rhinitis und des Bronchialasthmas sehr haufig verwendet, in einem geringen Ausmasse auch bei atopischem Ekzem Eine Hyposensibilisierung bei Lebensmittelallergien wird nicht durchgefuhrt.

Gesellschaften fur Allergie und Aufklarung in den Vereinigten Staaten Die zwei grossten nationalen Gesellschaften für Allergie sind in den Vereinigten Staaten die American Academy of Allergy und das American College of Allergists In beiden Organisationen gibt es ungefähr 1 00 Mitglieder es kommen aber doppelte Mitgliedschaften vor Es gibt uber 1500 Ärzte die sich auf Allergie spezialisieren das macht 1 p 100 aller tatigen Praktiker aus

Um anerkannter Spezialist fur Allergie in den Vereinigten Staaten zu werden muss man ein bis zwei Jahre — nach vorhergegangener abgeschlossener Ausbildung als Internist oder Padiater — an einem anerkannten Institut Allergie studieren Es gibt uber 30 Institute in den Vereinigten

Staaten die bewahrte Kurse fur Allergie teranstalten Es gibt aber nur 300 Ärzte die sich auf diese Weise augebildet haben

Die Allergy Foundation of America sieht als ihre wichtigste Aufgabe die Aufklarung der Allegmeinheit uber Allergie an Dies erreicht man durch Publikationen uber Heufieber Asthma und Kindheitsallergien durch Radio- und Fernsehreklame und Vortrage uber Allergie

Das National Institute of Allergy and Infectious Diseases leistet fundamentale Forschung auf dem Gebiete der Allergie und gibt auch Geld unterstutzungen an Einzelpersonne fur deren eigenen Forschungsprobleme Seit der Grundung dieses Institutes konnte mehr Geld fur die Allergieforschung und deren verwandte Gebiete aufgebracht werden als je zuvor

RESUMEN

Aproximadamente el 10 p 100 de la población de los E E U U padece de una forma mayor de alergia como asma rinitis o urticaria La alergia constituye la tercera enfermedad crónica en orden de importancia y causa una pérdida anual de 24 750 000 días de trabajo anuales

Los principales alergenos anemófilos varían grandemente debido a las diferencias geográficas y climáticas Probablemente el de mayor importancia sea el «ragweed» (Ambrosia) seguido de los polenes de gramíneas de árboles y los esporos de hongos Los hongos mas importantes son alternaria y Hormodendrum

Entre los alergenos perennes el polvo de casa desempeña sin duda e papel mas importante pero tienen también importancia los epitelios animales y las fibras de algodón Los alimentos como causa de alergia respiratoria especialmente en adultos no son muy comunes Como es bien sabido muchos asmáticos tienen alergias no demostrables con frecuentes infecciones de los senos o del árbol bronquial estos enfermos son llamados asmaticos «intrínsecos» y tienen asociada una eosinofilia de más del 10 p 100 y en general son de 40 a más años de edad Las alergias a medicamentosas más frecuentes son debidas a la penicilina y la aspirina

Diagnostico Un estudio alérgico completo incluye una cuidadosa historia clínica examen fisico radiografías de tórax y senos electrocardiogramas recuentos sanguíneos estudios del esputo y pruebas respiratorias funcionales Las pruebas cutáneas son de valor pero no deben sobreestimarse pues a menudo hay falsas reacciones positivas y negativas La práctica usual en E E U U es la de hacer una primera investigación por cutireacción seguida de pruebas intradérmicas con los alergenos requeridos En algunos casos se hacen directamente pruebas intradérmicas lo cual puede ser peligroso si previamente no se ha hecho una cuidadosa historia clínica Los extractos de polen y hongos utilizados son en general al 3 p 100 y 5 p 100 (porcentaje de material seco desengrasado con respecto al volumen de solución extractiva) en solución Buffer salina o en solución glicerinada Las pruebas cutáneas con extractos de alimentos dejan mucho que desear El mejor método para diagnosticar una alergia alimentaria es mediante las pruebas de eliminación Prácticamente las pruebas cutáneas con extractos bacterianos y de alimentos han sido abandonadas en E E U U

TRATAMIENTO ESPECIFICO La hiposensibilización (desensibilización) con inhalantes polenes y hongos se usa a menudo para el tratamiento del asma y la rinitis, mas raramente en el eczema Nunca se realizan desensibilizaciones en los casos de alergias alimentarias

SOCIEDADES Y EDUCACIÓN ALERGICA La dos sociedades mas importantes son la American Academy of Allergy y el American College of Allergists Cada una tiene aproximadamente 1200 miembros muchos de los cuales pertenecen a ambas Hay alrededor de 1500 médicos especialistas en alergia lo que representa el 1 p 100 del total de médicos

Para obtener el reconocimiento como especialista son necesarios dos años de estudio en un centro reconocido luego de finalizar la carrera Hay unas 30 instituciones con programas de especialización reconocidos y el numero de especialistas que han cumplido con todos los requisitos es de unos 300

La Allergy Foundation of America tiene como función primordial la educación popular sobre alergia la cual se lleva a cabo mediante folletos y programas de radio y televisión

El Instituto Nacional de Alergia y Enfermedades Infecciosas se ocupa de problemas de investigación en el campo de la alergia y también provee ayuda financiera a investigadores independientes Desde la creación de este Instituto los fondos destinados a la investigación en alergia han sido mayores que todos los destinados anteriormente

VENEZUELA

par

CARLOS BENAÏM PINTO M D

(Caracas)

L allergie considérée comme spécialite médicale bien définie et individualisée est tres récente au Venezuela En fait l allergie n a éte pratiquée jusqu a il y a peu de temps que par les dermatologistes et aussi en proportion mineure par les oto rhino laryngologistes les spécialistes de l appareil respiratoire et les pédiatres La conséquence immédiate de cet ordre de choses a été un très lent développement des études allergiques dans le pays et une méconnaissance de son énorme champ d action et de ses objectifs primordiaux non seulement par le public en général mais aussi par les médecins Sans exagerer on peut dire qu on a identifié — et beaucoup de personnes *identifient encore — l allergie avec un simple procédé de laboratoire qui* consiste à pratiquer quelques tests cutanes capables d etre effectués par n importe qui disposant du materiel nécessaire Il existe meme des « laboratoires spécialisés en epreuves allergiques » qui offrent leurs services aux médecins et procurent les antigenes nécessaires pour le traitement De tels établissements mais *aussi les medecins qui ont recours à leur service ignorent que le diagnostic et le traitement du malade allergique exigent quelque chose de plus que l usage de solutions antigeniques et de seringues hypodermiques* L existence de specialistes ayant une solide connaissance en médecine interne et un entrainement — clinique et expérimental — spécifiquement orienté vers les problèmes allergiques était virtuellement inconnue jusqu à il y a peu de temps au Venezuela

CONDITIONS ACTUELLES

Pour le million d habitants que compte Caracas il existe tout au plus quinze praticiens qui font de l allergie et parmi eux deux ou trois qui la pratiquent exclusivement La province manque virtuellement de spécialistes entraînés et les malades allergiques sont traités par les médecins praticiens ou les dermatologistes qui n étudient pas le patient allergique en tenant compte des progres considérables accomplis par l allergie dans les vingt ou trente dernieres années

Meme a Caracas il n existe pas de service spécialisé en allergie dans les etablissements de l Assistance Publique auxquels puissent avoir recours la grande masse de malades allergiques sans moyens suffisants pour se faire examiner et traiter à des consultations privees Leur traitement par les praticiens se réduit à une thérapeutique symptomatique par l usage des corticoides des antihistaminiques ou de topiques nasaux Des institutions comme la Sécurité Sociale soucieuses de faire parvenir l'assistance medicale a la masse ouvriere du pays manquent totalement de Services ou Consultations Externes d Allergie et leurs malades doivent etre adressés à des spécialistes prives

Bien qu on manque de données numériques sur lesquelles on puisse etablir des chiffres statistiques applicables a tout le Venezuela il est évident que le nombre de malades allergiques est tres eleve et peut etre meme superieur aux estimations faites aux États Unis Parmi les enfants la proportion de malades atteints d allergie cutanée et surtout respiratoire est considerable sans estimation de race ou de position sociale

L INFLUENCE DU MILIEU SUR LES MANIFESTATIONS ALLERGIQUES

Le Venezuela situe en pleine zone tropicale entre les 4^e^ et 12^e^ degres de latitude Nord avec une surface de presque un million de km² et des régions rurales très depeuplées presente de grandes variations de topographie qui commandent en partie les differences de son climat Les quatre saisons de climats tempérés n existent pas on peut distinguer seulement une saison seche et une saison de pluies Les conditions climatiques permettent l existence permanente de zones vertes et la floraison plusieurs fois par an des arbres des arbustes et des herbes

Comme les conditions du milieu ambiant ne sont pas connues a l interieur du pays les données suivantes ne s appliquent spécifiquement qu a la région de la capitale Caracas s eleve dans une grande vallee placee entre les chaines de montagnes qui sillonnent le nord du pays Son altitude (1 000 m) et la richesse de la végétation lui valent un climat modere pendant la majeure partie de l annee avec temperatures minimum de 15 20° C (60 68° F) et maximum de 30 35° C (86 95°) L humidité relative de l air varie entre 35 et 60 %

Des etudes sur les pollens atmospheriques n ont pas été sérieusement approfondies Elles se heurteront très probablement à la difficulté de ne pas avoir d époques définies de floraison L allergie pollinique existe surement, spécialement pour les graminées comme le prouve l existence de réactions cutanées positives

La recherche d autres agents étiologiques responsables de l allergie respiratoire dans la region de Caracas est en plein développement Des 1942 Di Prisco a établi la valeur de la poussiere de maison comme agent etiologique de l asthme bronchique Des études non encore terminées que j ai commencées il y a dix huit mois destinées à établir la flore mycologique de l air de Caracas et son rapport avec les cas cliniques d allergie respiratoire permettent d avancer des maintenant l influence des moisissures atmospheriques comme agents d allergie nasale et bronchique Les spores

paraissent etre présentes pendant toute l année dans l atmosphère avec prédominance de quelques genres pendant certains mois Enfin la valeur étiologique des émanations d insectes comme agents d allergie respiratoire a été analysee par l auteur à ce meme Congres Je les considere comme un facteur d importance dans l exploration allergique routiniere spécialement dans les pays tropicaux en considérant le fort pourcentage des sensibilisations par les malades étudiés

LA SOCIÉTÉ VENEZUELIENNE D ALLERGOLOGIE SES ACTIVITÉS

Avec l enthousiaste initiative du Dr A Perez Lozano la S V A s est constituée en 1956 peu apres son retour du 2e Congres de Rio de Janeiro Du fait de l absence d un nombre suffisant de specialistes en allergie la Société a éte formée de tous les medecins non specialistes interessés aux problèmes de l allergie Notre Societe bien que jeune s est montree vigilante pour ce qui touche aux intérets de l allergie et exige de ses membres un exercice professionnel digne de notre specialité Elle a tenté de susciter un interet pour l allergie dans le milieu médical national en faisant appel a des allergistes étrangers renommés pour exposer les progres de l allergie ainsi que ses problemes les plus importants Finalement elle travaille activement a la création de services specialisés dans les Instituts de l Assistance Publique ou pourront etre traites convenablement les malades allergiques sans ressources materielles ainsi que le secteur ouvrier de la population

Et pour terminer nous croyons qu on ne pourra susciter un interet majeur pour l allergie et ses problemes qu en réalisant les deux projets suivants *a*) par un enseignement donné aux jeunes étudiants pendant les cours universitaires et par des cours préparatoires pour les jeunes médecins *b*) par la divulgation des principes fondamentaux de l allergie dans le public médical et dans le grand public

a) L enseignement universitaire de l allergie a été néglige dans la plupart des Facultés de Medecine On a l impression que l allergie est consideree comme une simple curiosité physiopathologique destinee plutot a compléter le casse tete de quelques syndromes morbides et non pas comme affections ayant un mécanisme et une symptomatologie propres C est en raison de cette lacune dans leur éducation medicale que les jeunes médecins considerent avec un certain dedain l allergie comme spécialité médicale et inconsciemment la transforment en un pot pourri ou s assemblent tous les syndromes morbides d explication difficile Si par contre l etudiant était renseigné dès le début de sa carrière médicale de la portée et des buts déja atteints par l allergie ainsi que les nombreuses lacunes existant encore dans son étude les jeunes medecins deviendraient des praticiens bien avertis qui ne traiteraient plus leurs malades avec la médication symptomatique utilisée il y a cinquante ans lorsqu on ne disposait pas d autre traitement Il y en aurait certainement parmi eux qui interessés par les problèmes de l allergie se joindraient aux cliniciens et aux chercheurs qui s efforcent de résoudre les aspects obscurs de son mécanisme de son diagnostic et de son traitement

b) La meilleure connaissance des symptomes des méthodes de diagnostic, des formes de traitement, etc doit atteindre selon notre avis le grand public De meme que l'on a fait comprendre aux gens de s'abstenir de purgatifs en presence d'une symptomatologie abdominale aigue nous croyons fermement que ce meme public devrait etre averti qu'un asthme bronchique est une maladie allergique et non hépatique, et que les progrès modernes permettent dans beaucoup de cas l'établissement d'une étiologie precise Enfin il faut que le public sache qu'un traitement approprié permet a beaucoup d'asthmatiques de mener une vie normale semblable a celle des personnes non allergiques Malheureusement la divulgation scientifique a été utilisée par des individus sans scrupules pour servir leurs propres intérets Pour cette raison l'information scientifique devra etre confiée aux Societes scientifiques et les médecins responsables devront etre compétents et avoir une conduite professionnelle sans tache Finalement si l'on considere l'allergie comme un problème de santé publique — et je crois qu'il doit en etre ainsi — des organismes internationaux tels que l'Organisation Mondiale de la Santé pourraient contribuer activement aux campagnes d'information et recommander aux gouvernements des differents pays leur appui effectif a ces campagnes d'information publique

RÉSUMÉ

Le développement des études allergiques a été tres lent au Venezuela et son vaste champ d'action ainsi que ses objectifs primordiaux ont été méconnus non seulement par le grand public mais meme par les médecins Sans exagérer on peut dire que l'allergie est identifiee avec la simple application des tests cutanés L'existence de specialistes avec une solide connaissance en médecine interne et avec un entrainement clinique et expérimental spécifiquement orienté vers l'allergie était virtuellement inconnue jusqu'il y a peu de temps au Venezuela

Pour le million d'habitants que compte Caracas il existe au plus quinze praticiens qui font de l'allergie et parmi eux deux ou trois qui la pratiquent exclusivement La province manque virtuellement de spécialistes entraines et il n'y a pas de consultations externes d'allergie dans les établissements de l'Assistance Publique

Bien qu'on manque de données numériques sur lesquelles on puisse etablir des chiffres statistiques il est évident que le nombre de malades allergiques est tres éleve et peut etre même supérieur aux estimations faites aux États Unis

L'etude du milieu ambiant au point de vue allergologique est en plein developpement dans la région de Caracas, la capitale La valeur de la poussiere de maison comme agent étiologique d'asthme bronchique a éte reconnue en 1942 (Di Prisco) J'ai commencé moi meme il y a déjà dix huit mois l'étude de la flore mycologique et sa relation avec les cas d'allergie respiratoire et je peux assurer des maintenant le role des moisissures atmosphériques dans leur étiologie L'importance des émanations d'insectes a été

analysee à ce meme Congrès et je les considere d importance dans l exploration des malades allergiques surtout dans les pays tropicaux

La Société Venezuelienne d Allergologie s est constituee en 1956 sous l enthousiaste initiative du Dr A Perez Lozano Elle s est … vigilante en ce q…

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a) l enseignement des jeunes etudiants a l Université et la creation de cours preparatoires pour les jeunes medecins

b) l orientation et la divulgation des principes fondamentaux de l allergie dans le public medical et dans le grand public

SUMMARY

The notion of allergy has spread very slowly in Venezuela the public and even the physicians have for many years overlooked its essential features and underestimated its wide range of action

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In Caracas a city of a million inhabitants there are at the utmost 15 physicians practising allergology and only three outspoken specialists

The country practically lacks of specialists and there are no allergological medical advising centers in public hospitals

Although no statistical figure are available there is obviously a very large number of allergic patients and they run into higher figures than what has been estimated in the U S A

In the district of Caracas the capital the medicine is being intensively studied from the allergological point of view

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Active work is being done to create external consulting centers in public hospitals

b) La meilleure connaissance des symptomes, des méthodes de diagnostic, des formes de traitement, etc., doit atteindre, selon notre avis, le grand public. De meme que l'on a fait comprendre aux gens de s'abstenir de purgatifs en présence d'une symptomatologie abdominale aigue, nous croyons fermement que ce meme public devrait etre averti qu'un asthme bronchique est une maladie allergique et non hépatique, et que les progres modernes permettent dans beaucoup de cas l'établissement d'une étiologie precise. Enfin, il faut que le public sache qu'un traitement approprie permet à beaucoup d'asthmatiques de mener une vie normale semblable a celle des personnes non allergiques. Malheureusement, la divulgation scientifique a été utilisée par des individus sans scrupules pour servir leurs propres intérets. Pour cette raison, l'information scientifique devra etre confiée aux Societes scientifiques et les médecins responsables devront etre compétents et avoir une conduite professionnelle sans tache. Finalement, si l'on considere l'allergie comme un problème de sante publique — et je crois qu'il doit en etre ainsi — des organismes internationaux tels que l'Organisation Mondial de la Sante pourraient contribuer activement aux campagnes d'information et recommander aux gouvernements des différents pays leur appui effectif à ces campagnes d'information publique.

RÉSUMÉ

Le developpement des etudes allergiques a eté tres lent au Venezuela et son vaste champ d'action ainsi que ses objectifs primordiaux ont été méconnus non seulement par le grand public, mais meme par les medecins. Sans exagerer, on peut dire que l'allergie est identifiée avec la simple application des tests cutanes. L'existence de spécialistes avec une solide connaissance en medecine interne et avec un entrainement clinique et expérimental specifiquement oriente vers l'allergie etait virtuellement inconnue jusqu'il y a peu de temps au Venezuela.

Pour le million d'habitants que compte Caracas, il existe au plus quinze [illegible] qui la pratiquent [illegible] tra[illegible]és [illegible] [illegible]nts de l'Assistance Publique.

Bien qu'on manque de données numériques sur lesquelles on puisse etablir des chiffres statistiques, il est évident que le nombre de malades allergiques est tres elevé et peut etre meme superieur aux estimations faites aux États Unis.

L'etude du milieu ambiant au point de vue allergologique est en plein developpement dans la région de Caracas, la capitale. La valeur de la poussiere de maison comme agent étiologique d'asthme bronchique a été reconnue en 1942 (Di Prisco). J'ai commence moi meme il y a déjà dix huit mois l'étude de la flore mycologique et sa relation avec les cas d'allergie respiratoire et je peux assurer des maintenant le role des moisissures atmosphériques dans leur étiologie. L'importance des emanations d'insectes a ete

RESUMEN

El desarrollo de los estudios alérgicos ha sido muy lento en Venezuela y su vasto campo de acción así como sus objetivos primordiales han sido desconocidos no solamente por el publico en general sino tambien por los medicos Sin exagerar puede decirse que la alergia esta identificada con la simple realización de las pruebas cutáneas La existencia de especialistas con una sólida preparación en medicina interna y con suficiente experiencia clinica y práctica era virtualmente desconocida hasta hace poco tiempo en Venezuela

En Caracas con un millón de habitantes hay solamente quince medicos que hacen alergia de los cuales sólo dos o tres de manera exclusiva En el interior del país no hay prácticamente especialistas y en los establecimientos de la Asistencia Publica no hay consultorios externos dedicados a las enfermedades alergicas

Si bien no hay cifras sobre las que se puedan establecer estadisticas es evidente que la frecuencia de las enfermedades alergicas es elevada y tal vez superior a la frecuencia observada en los Estados Unidos de Norteamérica

El estudio de los alergenos ambientales de la region de Caracas está en pleno desarrollo La importancia del polvo doméstico como alergeno causante del asma bronquial ha sido reconocido en 1942 por Di Prisco y el estudio de la flora micologica ambiental iniciado por el autor hace diez y ocho meses indica que los hongos tienen un papel etiológico considerable Se considera asimismo la importancia de las emanaciones de insectos sobre todo en las zonas tropicales

La Sociedad Venezolana de Alergologia ha sido constituida en 1956 bajo la entusiasta iniciativa del D Pérez Lozano y se ha mantenido vigilante en todo lo que concierne al papel de la alergia y trata de atraer la atención sobre su importancia mediante conferencias periódicas de alergistas nacionales y extranjeros Trabaja asimismo activamente para promover la creacion de consultorios externos en los institutos de la Asistencia Publica

El interes que pueda suscitarse por la especialidad alergica reposa sobre dos principios la enseñanza dada en la Universidad y los cursos para post graduados y la divulgación de los temas de alergia entre los médicos y el publico en general

CHILE *

Zoltan BERNATH
(Cátedra de Introducción a la Medicina
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El Comite de Programacion del III Congreso Internacional de Alergia me ha encomendado la honrosa tarea de exponer a este Congreso la situación general y los problemas relacionados con el tratamiento y prevención de la enfermedades alergicas en Chile

Para abordar problema tan interesante me permitire exponer en primer lugar las condiciones geograficas climatericas y meteorológicas estrechamente vinculadas con la patogenia de las enfermedades alergicas

Geográficamente Chile es un país largo y estrecho que se extiende de Norte a Sur entre los paralelos 18 y 55 y de Este a Oeste entre el mar y la cordillera de los Andes que constituye las fronteras naturales hacia la Republica Argentina

La Republica de Chile es uno de los países más largos del mundo su longitud es de casi 5 000 kilómetros y por consiguiente tiene zonas climáticas muy variadas En el norte del país hay clima tropical y subtropical El centro del país posee un clima parecido al del Mediterráneo mientras que en el sur de Chile encontramos un clima frío y lluvioso parecido al de los países nórdicos

La población está constituída por los chilenos auténticos descendientes de los conquistadores españoles y por los descendientes de los inmigrantes de las diferentes razas en orden de importancia etnográfica son españoles alemanes italianos yugoeslavos árabes hungaros franceses ingleses noruegos rusos etc Cada nacionalidad y raza se ha ubicado en la zona geográfica y climática que más semejanza tenía consu país de origen

La población total de Chile asciende a 7 080 000 habitantes que se distribuyen a lo largo del territorio nacional pero sin lugar a duda preferentemente en la zona central cuya poblacion asciende a más de 3 000 Santiago bella capital de Chile tiene 1 500 000 habitantes

Por razones de la densidad demográfica nuestra exposición se va a referir especialmente a las condiciones de la zona central de Chile Esta zona consiste en mesetas verdes de abundantes aguas y de gran variedad de vegetación donde se encuentran casi todos los representantes de la flora de Europa y de Norte América Abundan las gramíneas y los árboles de

* Ce rapport nous étant parvenu tardivement il nous a été impossible d'en préparer les résumés

sombra y frutales Hay grandes extensiones de bosques naturales y plantados de pino y de eucaliptos Al clima de la zona central de Chile se adaptan fácilmente las plantas de Europa Este clima se caracteriza por veranos calurosos y secos sin lluvia, Hay grandes variaciones de temperatura en las 24 horas del día un día de verano puede ascender a 36° Celsius en el día y bajar a 10° Celsius en la noche Llueve únicamente en el invierno y la cantidad caída durante el año asciende sólo a 250-300 mm s que es una cifra bastante baja y no alcanzaría a los cultivos si no fuera por las abundantes aguas de riego provenientes de la nieve de las montañas que circundan el valle de la zona central En el resto del año que comprende 8 9 meses sólo llueve en forma excepcional unos pocos milímetros Esto constituye un factor muy importante en el problema de las alergias los árboles alergógenos siguen actuando mucho despues de la epoca de la polinización porque los pólenes quedan en parte adheridos a las hojas y frutos y en parte mezclados al polvo de las calles y de las habitaciones justamente por falta de la lluvia purificadora Por la misma razón los polvos y pelusas industriales provenientes de grandes hilanderías industrias químicas etc, contaminan al aire por largos periodos del año

POLINOSIS FN CHILE

Ha sido estudiado por médicos especialistas con la colaboración de botánicos de la Universidad de Chile y del Ministerio de Agricultura y se ha preparado la lista de las plantas alergogenas y un Calendario de Polinización para la zona central Además numerosas memorias de prueba se han dedicado al estudio de los pólenes y hongos recogidos en los anemopolinómetros y sobre la naturaleza antigénica netamente chilenas como el litre Por ser una planta netamente chilena y de gran poder alergógeno le daremos el sitio de honor en este resumen

Las diferentes tribus aborígenes que constituyeron la primitiva población de Chile conocían ya las propiedades del árbol originario del país llamado litre y sus efectos nocivos sobre el hombre Los araucanos consideraban que era un « árbol maligno» y siniestro en cuya sombra se enfermaba el que pasaba por allí La primera descripción fidedigna de la acción dañina del litre data del siglo XVII y fué hecha por el padre jesuíta Diego de Rosales Los conocimientos modernos sobre el litre se deben al Prof Alejandro Reyes quien en su magnífica monografía describe la historia, etiología patogenia y clínica de la «Enfermedad de Litre» En resumen los accidentes desarrollados en la especia humana bajo la acción de los principios tóxicos de la lithrea cáustica pertenecen a la categoría de las manifestaciones alergicas y son causadas por el contacto directo del árbol por sus pólenes, por sus resinas volátiles y aun por el humo de leña de litre o por la tierra de Litre» que como humus se usa extensamente en Chile como fertilizante de parques y jardines De aquí que las manifestaciones alérgicas al litre pueden producirse en cualquier epoca del año El cuadro clínico originado por el Litre corresponde a una dermatitis alérgica aguda y grave que se incluya no sólo en el sitio del contacto sino que se propaga en forma rápida en gran extensión y ataca de preferencia a los tejidos laxos formando grandes edemas de Quincke en los párpados escroto etc Hay compromiso del estado gene-

ral temperaturas altas leucocitosis etc La evolución espontánea puede ser de varias semanas y en la mayoría de las veces cura con restitución *ad integrum* Sin embargo puede tomar la forma de un eczema crónico que resiste a todo tratamiento sintomático Los enfermos quedan sensibles al litre toda la vida ya que el primer ataque no los deja inmunes

El tratamiento consiste en desensibilización específica para cuyo efecto se usan extractos acuosos de las hojas del litre que tienen mayor poder antigénico que los extractos de las fracciones liposolubles El resultado es espectacular ya a la primera o segunda dosis intradermica del antígeno se produce una remisión rápida de la sintomatología clínica y la evolución se acorta en muchos días ya que generalmente al cabo de 6 8 días de tratamiento el enfermo se halla asintomático No todas las personas son afectas a la acción del litre sino especialmente los alérgicos pero tambien es posible en individuos que nunca han presentado manifestaciones alergicas Se puede calcular que el 30 p 100 de todos los casos de dermatitis alérgicas en Chile son causadas por el litre

Para la determinación de las plantas más importantes en la etiología de la polinosis hemos estudiado más de 10 000 especies de las cuales se hizo la selección aplicando los cinco postulados de Thomen se han preparado más de 300 extractos de pólenes y se ha estudiado su actividad biológica en clínica Los resultados de esta investigación se aprecian en el cuadro Nº 1

La frecuencia de la polinosis en Chile es bastante considerable Alrededor del 4 p 100 de la población total está afectado Sin embargo existen polinosis endémicas tambien con una incidencia mucho mayor Así en el barrio Nuñoa de Santiago casi el 50 p 100 de la población está afectado por el polen del platanus occidentalis que florece en el mes de septiembre y causa estragos entre los vecinos del barrio

En una encuesta personal que practicamos recorriendo algunas calles casa por casa se pudo comprobar que en todas las casas había una o más personas que sufrían de fiebre de heno rinitis conjuntivitis o dermatitis en el mes de septiembre todos los anos debido a los polenes del plátano Sin embargo y a pesar de la evidencia clínica nunca hemos podido preparar un extracto verdaderamente activo del polen del plátano oriental y sólo obtuvimos reacciones cutáneas de mediana intensidad y resultados terapéuticos tambien medianos ¿A qué se debe este fracaso? dejo planteado este problema a los distinguidos especialistas que asisten a este gran Congreso Internacional de Alergia y pido su colaboración para la solución de este problema clínico y terapeutico tan importante para la salud de la población de Santiago de Chile

Otro aspecto interesante es la alergia industrial

El cultivo del cañamo y su consiguiente elaboración industrial han producido un problema sanitario importante por las manifestaciones morbosas que se han presentado en los numerosos obreros de esta industria

El Servicio Nacional de Salud pidió ayuda a nuestro Servicio de Alergia y hemos estado trabajando en los mismos terrenos de cultivo durante 6 semanas en la región de los Andes en colaboracion con el Dr Martini la putrefacción del cañamo se hace en grandes pozos artificiales donde el obrero trabaja sumergido hasta la cintura después el cáñamo se pone en fardos para secar al sol y al final pasa por la tascaduría donde se tritura el

cáñamo y se extrae la fibra Durante todos estos procesos mecanizados se produce gran cantidad de polvos industriales que el obrero inhala continuamente a pesar que se trabaja en galpones abiertos

Nuestros estudios demostraron la presencia de gran cantidad de esporas de hongos (aspergillus flavus penicilium sanguineum y rhizopus) que junto con los extractos del polvo del cañamo dieron cutirreacciones intensamente positivas en los obreros afectados Estos obreros sufrieron de un cuadro mórbido que comenzó a las pocas semanas de iniciado el trabajo y consistía en conjuntivitis y rinitis y una bronquitis de tipo asmatico Algunos obreros han presentado manifestaciones cutáneas de tipo alérgico como dermatitis por contacto y edemas Quincke de los parpados y escroto

Se ha comprobado que el 40 p 100 de los obreros estaba clínicamente enfermo 20 p 100 con manifestaciones asmáticas y 20 p 100 con otras alergias

Las cutirreacciones dieron resultados positivos en el 67 p 100 de los casos En todos estos se ha hecho tratamiento desensibilizante con muy buenos resultados clínicos el 72 p 100 de los enfermos desensibilizados pudo volver a su trabajo sin sufrir molestias alérgicas ulteriores durante el tiempo de observación de 2 anos

Así en esta forma la colaboracion de un servicio de alergia ha podido solucionar un problema de higiene industrial de primer orden

En Chile el problema general de la Alergia es semejante a otros paises si bien es cierto que el clima y condiciones de higiene ambiental e higiene industrial a pesar de los grandes progresos logrados favorecen y provoca enfermedades alergicas

El numero de personas afectadas es muy considerable y abarca todas las capas sociales de la población

Para la atención de las enfermedades alérgicas se dispone de la siguiente organización

Consultorios externos en las diferentes clinicas universitarias y hospitales, en Santiago tenemos 3 servicios de alergia y en provincias 4 servicios semi completos

El numero de especialistas en alergia es reducido debido a que en Chile no está reconocida como especialidad independiente sino como anexa a medicina interna

La Facultad de Medicina no tiene cursos especiales de alergia para los alumnos sino alguno de nosotros en calidad de Profesores Auxiliares hacemos 5 — 6 clases al año en los cursos regulares de medicina interna y de semiología

La Escuela de Post Graduados hace cursos cortos de alergia para medicos en Santiago y provincias

La Sociedad de Alergia de Chile está funcionando desde el año 1946 y actualmente tiene 8 miembros activos 6 especialistas de otros ramos que no pagan cuotas y 17 miembros honorarios que comprenden nuestros más distinguidos Profesores de la Facultad de Medicina de la Universidad de Chile

SUISSE

par

Georges BICKEL
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Les aspects médico sociaux des maladies allergiques peuvent être envisagés de deux façons différentes selon qu on considère le rôle tenu par les facteurs sociaux dans la genèse des affections allergiques ou selon qu on étudie les répercussions sociales de ces affections en tant que facteurs de mortalité et d incapacité de travail

Il a été souvent répété que les maladies allergiques étaient des « maladies de la civilisation » Cette affirmation n est pas complètement exacte Les Anciens connaissaient plusieurs des affections auxquelles nous attribuons aujourd hui une origine allergique et ces mêmes affections s observent bien qu avec une fréquence moins grande qu en Europe et aux États Unis d Amérique chez diverses peuplades demeurées primitives Le mot grec asthma qui signifie halètement se trouve une dizaine de fois dans l œuvre d Hippocrate et Arétée au milieu du second siècle de notre ère a donné de la crise d asthme une description qui est demeurée classique Il n en est pas moins vrai que la nature de plus en plus artificielle de notre alimentation la pollution de plus en plus marquée de l atmosphère et l utilisation industrielle sans cesse grandissante de corps chimiques nouveaux ont développé dans une mesure considérable le nombre des antigènes auxquels l homme est susceptible de se sensibiliser

Beaucoup plus agressive encore que ces facteurs généraux de sensibilisation la chimiothérapie moderne avec sa création quotidienne de plusieurs douzaines de produits nouveaux est devenue la grande pourvoyeuse de maladies allergiques La plupart de nos médicaments synthétiques actuels sont en effet susceptibles dans certaines conditions et surtout chez certains sujets prédisposés de jouer le rôle d allergènes complets ou partiels et leur introduction en thérapeutique a provoqué en plus d une floraison particulièrement abondante de manifestations allergiques classiques l apparition de plusieurs syndromes nouveaux tels que l agranulocytose et diverses hémopathies thrombocytopéniques et hémolytiques syndromes qui sont le résultat indiscutable d un processus immunologique de nature allergique

En dehors des allergènes eux mêmes certains facteurs d ordre social jouent dans la production des réactions de sensibilisation un rôle qui ne

doit pas etre sous estimé On a souvent signale que les classes intellectuellement et socialement les plus elevées comportaient une proportion particulierement forte de sujets allergiques La statistique d ailleurs discutable de Clarkson (1937) indique parmi 300 asthmatiques de moins de vingt ans 75 p cent d eleves au dessus de la moyenne 24 p cent d éleves moyens et 1 p cent seulement d eleves mediocres

On sait d autre part que la frequence du rhume des foins est notablement moins grande dans la population des campagnes que dans les populations urbaines Il est vrai que cette discordance peut s expliquer par le fait que le contact repete avec les allergenes constitue un facteur de désensibilisation tandis que les contacts intermittents s ils n exasperent pas toujours la sensibilite s opposent dans la regle à son attenuation

Quant aux facteurs psychosomatiques et emotionnels dont l intervention est certainement plus frequente chez les gens cultivés que chez les illettres ils ne jouent qu un role secondaire en ce qui concerne le proc ssus de sensibilisation lui meme Ils presentent en revanche, une grande importance en tant qu elements de declenchement ou d aggravation des paroxysmes chez les sujets sensibilises comme le prouve l exemple bien connu de Trousseau On sait d autre part que la poussee d urticaire declenchee par l ingestion occasionnelle de homard ou de moules peut se perpetuer durant de nombreux mois alors que le sujet n a plus eu le moindre contact avec l allergene nocif et que son organisme peut en etre considére comme debarrassé L intervention du systeme nerveux, et plus particulierement du systeme neuro vegetatif contribue activement a ce phenomene de persévération

Les repercussions sociales des maladies allergiques ont eté jusqu ici beaucoup moins etudiees que le role des conditions sociales dans la genese de ces affections Quelques statistiques interessantes ont pourtant ete publiées aux Etats Unis d Amerique et en Angleterre statistiques qui étudient plus particulierement l importance de l asthme comme facteur de mortalite et d incapacité de travail

Ces statistiques sont en bon accord en ce qui concerne la mortalité de l asthme Un peu moins du 1 p cent des deces — en prenant les moyennes de dix ans — sont dus à l asthme ceci aux États Unis d Amerique comme en Angleterre et en Sui se Mais tandis que la proportion des déces dus a l asthme parait avoir diminue d un peu plus d un tiers dan les pays anglo-saxons le phenomene inverse a été enregistre en Suisse Il est toutefois probable que cette discordance est plus apparente que réelle et qu elle tient en partie a la façon dont sont pratiquées les enquetes Il e t en effet souvent difficile d apprecier si la cause du deces d un asthmatique est due a l asthme lui meme ou s il faut l attribuer surtout a l emphys me a l insuffisance cardiaque ou a la bronchopneumonie qui se sont greffés sur l asthme

En dehors de l asthme les maladies allergiques classiques telles que le rhume des foins les urticaires et la migraine ne présentent qu une importance sociale mineure du fait que la mortalité en est insignifiante et que les progres réalises dans le traitement de ces affections ont réduit a un minimum les jours d incapacite de travail qui en sont la consequence Il n en est pas de meme des dermatites du contact qui provoquent souvent des incapacites de travail prolongees et peuvent contraindre à des changements de profession

Beaucoup plus grande cependant est l importance sociale des allergies

medicamenteuses rançons inevitables des progres th rapeutiques de notre siecle Elles frappent dans le monde des centaines de milliers de sujets compliquant l évolution de leur maladie retardant leur convalescence et posant frequemment de difficiles problemes de traitement Elles peuvent

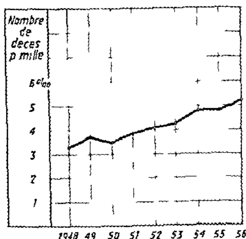


FIG 1 — Stat st que des déc s par asthme en Suisse de 1948 a 1956 (asthme considere comme cause prima re de la mort)

meme aboutir tel le choc anaphylactique penicillinique a un exitus quasi foudroyant Lorsqu on substitua il y a une douzaine d annees la penicilline aux sulfamides en vue du traitement des infections a streptocoques et a pneumocoques on nourrissait l espoir de supprimer l inconvenient majeur

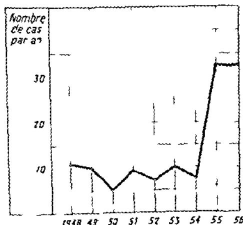


FIG 2 — Nombre d ujets hospital a la Cl n que m d cale de Geneve de 1948 à 1957 pour allergies med camenteu es graves

des dérivés de la sulfanilamide qu'on considérait comme trop allergisants. Espoir rapidement déçu puisque plusieurs centaines d'individus, victimes d'accidents anaphylactiques mortels, payent chaque année leur tribut à la « reine des antibiotiques ». Constatation d'autant plus navrante que la plupart des malades ainsi frappés avaient reçu l'injection meurtrière à l'occasion d'un état infectieux bénin pour le traitement duquel l'emploi de la pénicilline était, sinon contre-indiqué, du moins superflu.

Si les antibiotiques et les sulfamides constituent les facteurs les plus importants des réactions médicamenteuses aujourd'hui observées, c'est d'ailleurs plus en raison de l'énorme fréquence de leur emploi qu'en raison d'une intensité particulière de leur pouvoir allergisant. D'autres produits moins utilisés sont à ce point de vue plus nocifs et il n'est guère de médicament de nos pharmacopées modernes qui ne puisse être la cause d'une réaction allergique occasionnelle. L'agressivité de la pénicilline tient à la trop grande facilité avec laquelle les médecins la prescrivent et les malades la réclament. Parmi 100 adultes que nous avons récemment interrogés, il n'en était que 18 qui n'avaient jamais reçu de pénicilline et, parmi les 82 qui en avaient reçu, 8 seulement avaient souffert d'une maladie pour le traitement de laquelle l'indication de la pénicilline était indiscutable.

C'est dire qu'une plus juste estimation des indications thérapeutiques constituera le meilleur moyen — et peut-être le seul moyen — d'éviter que les médications modernes, fierté justifiée de notre siècle, ne prennent rang parmi les causes majeures de la morbidité humaine.

RÉSUMÉ

Les maladies allergiques ont pris, du fait de l'orientation de notre alimentation et de l'utilisation industrielle ou thérapeutique d'une *foule de produits* nouveaux, une importance de plus en plus prépondérante. Celle-ci se manifeste non seulement par une abondante floraison de *réactions allergiques* classiques, mais aussi par l'apparition de syndromes *nouveaux* tels que l'agranulocytose et diverses hémopathies hémolytiques ou *thrombocytopéniques*.

Les facteurs sociaux qui ont entraîné la diffusion des *états allergiques* interviennent également dans la prédisposition à ces états. *Les classes* intellectuellement et socialement les plus développées sont *en effet frappées* de façon élective et il n'est *pas* douteux que les facteurs psychosomatiques et émotionnels, qui ne jouent qu'un rôle secondaire *en tant qu'agents* de sensibilisation, présentent une grande importance comme *éléments* de déclenchement ou d'aggravation des paroxysmes chez les sujets sensibilisés.

Les maladies allergiques, d'autre part, comportent *d'importantes* répercussions sociales non seulement comme facteurs de *mortalité*, mais plus encore en tant que facteurs d'incapacité de travail. Alors que l'asthme occupait à ce point de vue, jusqu'il y a peu d'années, une *situation dominante*, ce sont aujourd'hui les allergies médicamenteuses, *rançons inévitables des* progrès thérapeutiques de notre siècle, qui l'ont supplanté dans ce rôle. *Les*

sulfamides et les antibiotiques se sont révélés du fait de la généralisation de leur emploi particulièrement agressifs et sont responsables de nombreux décès dont beaucoup sont malheureusement dus à des applications abusives de ces produits

SUMMARY

During the last years allergic diseases have become more and more prevalent in connection with the changes in our food and also with the increasing use of industrial and therapeutic chemical compounds

The clinical manifestations of allergic syndromes are characterized not only by the classical reactions but also by the appearance of new syndromes such as agranulocytosis various hemolytic or thrombocytopeni hemopathias

Social factors have contribued to the diffusion and also to the predisposition to the increase of allergic states The intellectual and more socially advanced classes are electively affected with this type of disease and there is no doubt that emotional and psychosomatic factors while playing only a minor role as sensitization agents do have a great importance as eliciting and aggravating factors in allergic patients

On the other hand allergic diseases have important social repercussion not only as causes of death but also as causes of loss of work While asthma has been the prevalent disease in this respect until the last years drug reactions are now becoming the main cause of allergic reactions due to the abusive use of therapeutic agents Sulfonamides and antibiotics appear to be particularly agressive and responsible for numerous death cases of which many are due to useless applications of these drugs

ZUSAMMENFASSUNG

Die allergischen Erkrankungen haben an Bedeutung steigend zugenommen im Hinblick auf unsere Ernährung und auf die industrielle und therapeutische Anwendung von Unmengen neuer Produkte Abgesehen von den klassischen allergischen Reaktionen in weitester Verbreitung gibt es auch gewisse neue Syndrome wie die Agranulozytose und verschiedene hämolytische Hämopathien oder Thrombozytopenien

Soziale Umstände die einerseits die Verbreitung allergischer Zustände zur Folge haben bedingen in gleichem Maße ihre Disposition So sind zum Beispiel die intellektuel und sozial besonders hochstehenden Klassen nahezu elektiv betroffen und es besteht kein Zweifel daß psychosomatischen und emotionellen Faktoren die im Hinblick auf die Sensibilisations mittel nur eine zweitrangige Rolle spielen eine große Bedeutung bezüglich der Auslösung oder Verschlimmerung der Anfälle bei sensibilisierten Kranken zukommt

Die allergischen Erkankungen erlauben andererseits wichtige soziale Rückschlüsse nicht nur in Bezug auf die Mortalität sondern vor allem im Zusammenhang mit Arbeitsfähig = bzw unfähigkeit Von diesem Gesichtspunkt aus kam dem Asthma als solchem bis vor wenigen Jahren eine überragende Stellung zu Heute sind es jedoch die medikamentösen

Allergien die es — die therapeutischen Fortschritte unseres Jahrhunderts stark beeinträchtigend — aus dieser Rolle verdrängt haben. Sulfonamide und Antibiotika haben si[illegible] Anwendung als besonders aggressiv herausg[illegible] licherweise für zahlreiche [illegible]

RESUMEN

Debido a la orientación de nuestra alimentación y a la utilización industrial y terapeutica de una gran cantidad de sustancias nuevas, las enfermedades alergicas han tomado una importancia cada vez mayor. Esto se manifiesta no solamente por el aumento de las reacciones alergicas clásicas sino también por la aparición de síndromes nuevos como la agranulocitosis y diversas hemopatías hemolíticas o trombopenicas.

Los factores sociales que han acarreado la difusion de los estados alergicos intervienen asimismo en la predisposición a esos estados. La clase intelectuales y de mejor condición social son, en efecto, las mas afectadas. No hay duda que los factores psicosomáticos emocionales, que desempeñan un papel secundario como agentes de sensibilización, presentan una gran importancia en la aparicion y agravación de los síntomas en los sujetos sensibles.

Por otra parte, las enfermedades alergicas tienen gran repercusión social no sólo como factores de mortalidad sino especialmente como factores de incapacidad de trabajo. En tanto que el asma ocupaba hasta hace pocos años una posicion dominante desde ese punto de vista, actualmente son las alergias medicamentosas, consecuencia inevitable del progreso terapeutico de nuestro siglo, que lo han suplantado. Las sulfamidas y los antibióticos son especialmente agresivos y, dado su uso generalizado, son la causa de muchos accidentes fatales provocados a veces por su empleo abusivo.

FRANCE

par

Pierre BLAMOUTIER

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C'est en France que Richet et Portier découvrirent en 1902 l'anaphylaxie.

C'est en France qu'en 1914, les premiers, Widal et ses collaborateurs démontrèrent que certains asthmes et certaines urticaires étaient des syndromes relevant d'un mécanisme comparable à celui que l'on observe dans l'anaphylaxie expérimentale.

Personne, à l'époque, n'aurait pu soupçonner toute l'importance qu'allaient prendre en clinique les *affections allergiques*. La notion d'allergie a été appliquée depuis lors en effet à de nombreux faits observés dans tous les domaines de la pathologie.

Certaines de ces maladies peuvent avoir des répercussions sociales et économiques très étendues. Ce seront surtout celles dont les manifestations sont d'ordre *respiratoire* (asthme nasal et trachéo-bronchique) et *cutané* par allergie tissulaire (dermites) plus que par allergie humorale (urticaire, œdème de Quincke et certains eczémas).

Les manifestations allergiques d'origine *digestive* (certaines gastrites et colites), *nerveuse* (divers cas de migraine), *oculaire* (quelques conjonctivites), *rénale* (les néphrites streptococciques notamment), *articulaire*, *cardio-vasculaire*, *sanguine* ne peuvent pas être considérées comme susceptibles d'avoir dans ce domaine un semblable retentissement.

Si les représentants de quarantes Nations qui prennent part à ce Congrès ont sur les diverses affections allergiques des conceptions théoriques qui doivent être assez voisines, ils peuvent avoir par contre à leur sujet tant au point de vue social qu'économique des opinions différentes qui méritent d'être exposées en commun.

La France fut le berceau de l'anaphylaxie, donc de l'allergie. Jusqu'à ces dernières années néanmoins, rares furent les médecins français qui s'occupèrent des divers problèmes que l'allergie allait poser en clinique.

Actuellement leur nombre va croissant Mais les specialistes en allergologie restent exceptionnels Cette branche de la medecine n est pas consideree en France comme une specialite elle n est d ailleurs pas reconnue par l O dre National des Medecins ni par la Securite Sociale Beaucoup parmi les medecins qui s intéressent specialement aux questions allergiques exercent la médecine générale les autres sont des pneumologues des pediatre des dermatologues mais ils ne sont pas des allergologues spécialises Aussi conservent ils l esprit clinique et critique fait de bon sens du medecin qui ne rapporte pas comme de nombreux speci listes toutes les m nifestations pathologiques qu ils observent a la seule spécialité qu ils exercent

La premiere consultation des maladies allergiques ouverte dans les hopitaux parisiens (service du Professeur Pasteur Vallery Radot) ratt chee actuellement a la Clinique Propédeutique de l Faculte de Médecine d Paris a reçu, depuis trente quatre ans un grand nombre de m l des presentant des affections allergiques les plus diver es Plusieurs milliers y ont subi ces dernieres années un traitement regulier de désensibilisation spécifique

D autres consultations hospitalieres ont eté ouvertes ces dernieres annees a Paris et dans certaines villes de province Marseille Borde ux Reims Strasbourg notamment Elles y reçoivent de nombreux malades et sont en plein développement

La plupart des medecins français devenus allergologues ont freq enté les écoles parisiennes d Pasteur Vallery Radot et de Tzanck promoteurs en France de l allergologie

Un cours annuel destine aux médecins qui s interessent à l allergologie e t donne chaque annee a la Clinique Propédeutique de l F culte de Medecine d Paris Le Professeur Pasteur Vallery Radot et ses collaborateurs y expos nt le divers sujets se rapportant a la partie clinique Halpern et ses eleves y traitent en det il l allergie et l immunologie expérimentale

La *Securite Sociale* ne comprend pas toujours en France toute l importance des soins donnes par le medecin allergologue le diagnostic exact qu il porte d une dermatose ou d un asthme allergique dont la nature a ete jusqu alors meconnue certaines thérap utiques dél cates qui ne sont pas toujours exemptes de danger telle la désensibilisation faite avec cert ins extraits allergeniques La *valeur de l acte professionnel allergologique* n a souvent guere plus d importance a ses yeux qu un diagnostic d angine ou de bronchite ban le qu une prise de sang pour un examen biologique Et pourtant comme l absenteisme pourrait etre réduit comme de nombreux medicaments d un prix élevé ne seraient pas aussi facilement prescrits combien de mises en « Longue Maladie » ou en « Invalidite » seraient évitees si le médecin ne se contentant pas de porter seulement le diagnostic simptomatique d asthme cherchait toujours a en connaître l origine si souvent allergique! Nombreuses sont les observations qui le prouvent *Une parmi* tant d autres va nous permettre de montrer toute la valeur sociale et son retentissement économique d un di gnostic étiologique correctement porté

Une jeune fille de v ngt uatre ans asthmat que d pu s l age de v ngt ans a a t des cr ses quot d ennes qu ne se produ s ent qu a son dom le fam l al Elle n a a t jama s benefic des multiples tra tements qu on lu av t fa t s a re ceux c ne cons sta ent d a lleurs qu en med cat ons symptomat ques atte gnant des sommes fort elevees remboursees par la Secur te Soc le a 80 p 100 au debut pu s en total te Cette jeune fille total sa t en qua re ans 5 8 jours d arret de tra a l Des cures thermales lu furent prescr tes elles resterent nefficaces pu sque la m lade n a a t des cr s s d asthme que chez elle On l a a t m se d s l tro s eme annee a l a uran e longue malad e   donc avec la cou erture ntegr le de tous ses fra s Ce fut a l occas on de l « Assurance In a d te   d scutee a son sujet que le medec n expert en pneumo ogie de la Securite So ale demanda mon a s sur son cas

Or dans l loge de concierge de ses parents v a ent tro   chats Une cut react on fa te ec un extr t de po ls de cl at fut extremement pos t e ell me montra que le d agnost c et olog que d asthme alle g que a ces phaneres eta t certa n

Pour obten r d s paren s l éloignement des ch ts et le netto age so gne de la loge a l asp r teur toutes fenetres ou ertes il fallut que le medec n exp rt menaçat l nteressée de lu fa e suppr mer tout remboursement de ses fr s de mal d e Des que les chats d sparurent de la loge et que l asp rat on des po ls qu ils y a a ent semes depu s de nombreuses annees f t fa te les cr ses d asthme cessèrent auss tot et la malade put reprendre sans dela   norm lemen son tra a l

P r su   de la meconna ssance d un d agnost c et olog que qu l eta t pourtant fac le de porter le cas de cette jeune fille couta fort cher a la Securite Soc le il r squa t de l entra ner encore pour une du ee ndéter m nee dans des fra s cons d rables

Jusqu a c s dern   res annees nous et ons en France tr but res des pay etrangers pour la fourn ture c s ext a ts allergen ques dest nés à fa re des tests cutanes (cuti et intradermo react ons) ou a tra ter les mal des par une désens b l at on spéc fique Aucune firme franç se ne f b qua t en effet ces produ ts

Depu s deux ans l In t tut Pasteur prepare une sér e d extra ts allerge n ques des nés au d   c et au tra tement des malad es allerg ques   l rend un grand serv ce aux méde ns allergologues qu peuvent a ns se procurer d excell ntes prep rat ons   s ns attend e pendant longtemps vu les d ffi ultes douan ere   ren ontrees auxquelles s ajouta ent sou ent de problemes monet   es la l ra son de produ ts qu leur sont nd spen sables

L asthme bronch que p ra t etre en France en progress on constante m s aucune st st que n permet de prec ser le nombre des   sthmat ques qu v   ent sur notre sol Parm les sujets qu   présentent un asthme réel quell   peut etre la p oport on de ceux qu   souffrent d un astl me dont la nature allerg que peut etre reconnue   Nous pens ons a ec Pasteur Vallery

Radot il y a une vingtaine d années qu elle ne dépassait pas 10 à 15 p 100 Grâce à la pratique systématique des tests cutanés faits actuellement chez tous les asthmatiques que nous examinons des intradermo réactions en particulier à la poussière de maison aux objets de literie aux moisissures ou à tous autres pneumallergènes que l interrogatoire peut faire supposer responsables nous croyons maintenant que près des deux tiers des asthmatiques que nous observons adultes et enfants sont atteints d asthme allergique

L observation de l enfant permet de voir se dérouler sous les yeux du médecin les différentes étapes sociales de l allergie Le plus souvent prédisposé *par son hérédité le petit asthmatique s est d abord* sensibilisé à des trophallergènes (lait farine blanc d œuf) puis un peu plus tard aux pneumallergènes observés chez l adulte Ceux ci sont intervenus différemment suivant l habitat le climat les saisons la profession des parents

La suppression de l allergène responsable et une désensibilisation spécifique permettra au début de laisser le petit asthmatique dans son milieu habituel familial et scolaire Mais le plus souvent ce traitement ne suffit pas il deviendra nécessaire d éloigner l enfant des locaux fréquemment insalubres où il vit des centres urbains souvent industriels qu il habite vers des régions moins humides plus ensoleillées à la campagne au bord de la mer surtout à la montagne aux environs de 1 200 mètres si possible altitude où l on ne rencontre plus qu *exceptionnellement* l allergène poussière de maison le plus souvent responsable de l asthme allergique chez l enfant

C est à ce moment que l assistante sociale pourra être une auxiliaire fort précieuse pour le médecin en fournissant à la famille du jeune asthmatique tous les renseignements nécessaires au sujet des décisions thérapeutiques qui s imposent admission dans les *maisons d enfants* et *établissements à caractère sanitaire* permettant des séjours prolongés (sur les côtes d Azur et Atlantique dans les Alpes) *internats privés* (Abondance Villard de Lans Font Romeu Chamonix) *lycées climatiques* (Briançon notamment) *placement familial* dans les villages de montagne Il n existe en France qu un petit nombre de maisons de cure spécialisées *ne recevant* que des enfants asthmatiques il est souhaitable que les *administrations* d assistance et de sécurité sociale s intéressent à la création de centres climatiques particuliers pour cette catégorie de malades (affectation d anciens sanatoria qui ne reçoivent plus de malades tuberculeux par ex) L amélioration rapide de l état de santé de ces jeunes asthmatiques allergiques obtenue dans *des conditions d existence nouvelle au moment de leur croissance* permettrait à ces enfants qui seront bientôt des adolescents de ne pas devenir ces asthmatiques adultes bronchitiques si souvent tôt ou tard emphysémateux même scléreux pulmonaires voués à une infirmité qui pourra devenir permanente et définitive par conséquent incapables désormais de travailler avec régularité encombrant souvent les hôpitaux et restant ainsi pendant de nombreuses années à la charge de la Société

Dans le domaine de l allergie une notion domine toute autre au point de vue social celle de la *maladie professionnelle* Le travailleur qui présente

a l occasion de sa profession un asthme bronchique ou une dermite par contact est il atteint d une affection allergique due au terrain particulier qui le predispose ou s agit il chez lui d un accident du travail ? En etudiant successivement chez l ouvrier l allergie respiratoire de l adulte et l allergie cutanée nous allons voir comment en France peut se poser cette question

L asthme professionnel retient specialement l attention de medecins du travail et des employeurs dans les professions ou il est particulierement observe comme il doit interesser les organismes de Securite Sociale ses consequences sont en effet tres importantes tant du point de vue économique que social

Quelle est la part de l allergie dans l asthme professionnel ? Le travail engendre certainement plus de cas d asthme non allergique consecutifs a l irritation tracheo bronchique que provoque l inhalation de poussieres de gaz et de vapeurs que d asthmes allergiques Chez un certain nombre de ceux ci une sensibilisation se greffe secondairement sur la muqueuse irritee l antigene sensibilisant dans ce cas n est pas une substance pro teique il peut etre considere comme un haptene qui ne devient antigenique que par couplage avec une proteine de l organisme Plus rarement l asthme professionnel sera de nature essentiellement allergique comme chez le boulanger sensibilise a la farine qu il inhale dont l asthme persi tera pendant toute la duree de son travail et cessera des son eloignement du fournil Cet asthme professionnel du a une sensibilisation de nature pro teique restera un asthme allergique pur vu l absence de toute irritation tracheo bronchique provoquee comme dans les ca precedents par d inces sants microtraumati mes locaux

Il se pose pour l asthme le probleme que nous retrouverons dans les der matoses allergiques du travail Selon le metier exerce on pensera a des allergenes *habituels* poussiere de textile vapeurs de colorants de synthese produits pharmaceutiques (antibiotiques et antihistaminiques) matieres plastiques etc mais les allergenes *occasionnels* beaucoup plus nombreux soulevent des problemes encore plus difficiles a resoudre car il peut s agir d une sensibilisation a un produit intermediaire entre la matiere première et le produit termine

Nous pensons qu au point de vue social les conclusions suivantes peu vent etre formulees a propos de l asthme professionnel allergique

1° Survenant habituellement chez un predispose il est plus souvent *indi viduel* que *collectif*

2° La constatation de l arret des crises quand l interesse cesse son travail et de leur reapparition des qu il le reprend peut etre considérée comme l unique preuve de la nature allergique d un asthme professionnel Les tests cutanés inconstants dans les indications qu ils peuvent donner n ont pas la valeur de ce *test direct*

3° Le diagnostic d asthme professionnel allergique porte l ouvrier devra etre change de poste si son activite l expose à une irritation permanente de la muqueuse trachéo bronchique car il y a tout lieu de craindre que l asthme persévere donc s aggrave si la cause qui le déclenche persiste

La mutation de poste est souvent difficile car il s agit habituellement d ouvriers qualifiés dont le reclassement peut entraîner une diminution de salaire ce sera le cas par exemple de l infirmière soignante devenue allergique aux antibiotiques qui ne pourra plus occuper qu un poste administratif

4° Le changement d emploi devrait être indemnisé si l ouvrier est obligé de quitter définitivement son métier Mais cette indemnisation qui s r it équitable n est pas encore prévue par la loi française

Les *dermatoses par sensibilisation* constituent avec l asthme et ses équivalents respiratoire les manifestations les plus fréquemment observées en allergologie Elles doivent être bien connues du médecin praticien du médecin d entreprise

En France leur étude a été faite en particulier par Tzanck et Sidi Sous leur impulsion diverses consultations hospitalières de dermato allergie ont été ouvertes depuis une quinzaine d années Il existe actuellement à Paris un service dirigé par Sidi (Fondation de Rothschild) qui a reçu en 1957 plus de 16 000 consultants dont la plupart y ont été adressés par des médecins d usine

Ce sont en effet les dermatoses réactionnelles d origine professionnelle qui sont les plus fréquemment observées Le médecin pensera surtout à leur nature allergique si la dermato e présente les caractères d une dermite artificielle ou chaque fois que le malade déclarera que son « eczéma » est apparu au cours de ses occupations professionnelles

L apparition d une dermatose qui se sera développée à l occasion du travail po e au point de vue médico social un problème complexe Il est d s dermatoses secondaires à un traumatisme à une infection à une irritation à une action caustique ces manifestations sont indemnisées comme des accidents du travail (loi de 1898) Mais la plupart des dermatoses professionnelles allergiques moins favorisées relèvent des lois sur les a ur nces sociales (lois de 1928 1930) Une dermite provoquée chez un ouvrier coiffeur par l application d une teinture à la paraphenylènediamine est un accident du travail Mais si cette dermite est consécutive à l emploi d un schampoing ou d une permanente à froid ce même ouvrier ne touchera plus que les prestations des assurances sociales

Les ouvriers qui manipulent le ciment le nickel les dérivés de l aniline l infirmière qui présente une dermite causée par la manipulation de la streptomycine sont indemnisés en accident du travail mais par contre une dermatose provoquée chez celle ci par le contact de la pénicilline ou de la chlorpromazine ne donnera droit qu à l indemnité de l assurance maladie

En France l indemnité journalière de « l Assurance Maladie » correspond à la moitié du gain journalier de base à partir du quatrième jour de la maladie et pendant six mois au maximum Les frais médicaux et pharmaceutiques sont remboursés pendant ce temps à 80 p 100

L indemnite « Accident du Travail » correspond des le premier jour et pendant le premier mois à la moitié du salaire a partir du second mois aux deux tiers de celui ci jusqu a la guérison Elle peut etre majoree dans certains cas au dela du troisieme mois L accidenté a droit a la couverture de tous ses frais medicaux et pharmaceutiques

La cause la plus frequente des allergies cutanees decoule de l extension toujours croissante des industries chimiques Aussi les dermites par contact s observent elles surtout chez les ouvriers qu elles emploient assez souvent chez les femmes qui se servent de cosmetiques ou chez les ménageres utilisant certains produits d entretien etc Or la liste des substances chimiques considérees comme nocives ne comporte en France qu un nombre restreint de produits Les ouvriers qui presentent une dermite d etiologie allergique reçoivent une indemnite qui est variable suivant le produit responsable La loi ne devrait pas etre aussi limitative Une loi juste devrait dedommager de la meme façon toutes les dermites professionnelles de nature allergique Une telle loi permettrait d avancer la solution de problemes d ordre social qu il est important de resoudre en tenant compte des différents facteurs qui sont à leur origine

Les incidences medico sociales des dermatoses allergiques sont aussi importantes pour le malade et pour son entourage que les répercussions économiques qu elles entrainent (nombre tres élevé des journées d arret de travail perte considerable de salaires) le sont pour le Pays Pour remédier a ces consequences tous les moyens de diagnostic et de traitement doivent etre étudies toutes les mesures de prevention individuelles et collectives doivent etre prises

En conclusion de cet exposé il y a lieu d attirer tout specialement l attention des organismes responsables de la Santé Publique et de la Sécurite Sociale sur l importance médico sociale des problemes que pose l allergie et leur retentissement sur l économie nationale

Les moyens de lutter contre l allergie respiratoire et cutanee en particulier resident avant tout dans le *depistage* (interrogatoire tests cutanés et cliniques necessitant la coordination des efforts du medecin du travail du medecin de la Sécurité Sociale et du médecin allergologue) dans la *prevention* (sélection a l embauchage surveillance systématique reclassement suppression du risque allergique) dans la *protection* de tous les sujets exposés à une sensibilisation au cours de leur travail comme dans les *traitements* appropriés qui devront etre appliques

Le malade atteint d asthme bronchique ou de dermatose professionnelle dont l origine allergique n aura pas éte reconnue assez tot subira toutes les consequences d un diagnostic tardif qui au lieu d etre *étiologique* n aura éte trop longtemps que symptomatique en tant que travailleur dont l activite se trouvera progressivement diminuee puis arretee en tant que soutien de famille s il est marie s il a des enfants qu il ne pourra plus faire vivre aidé toutefois par les allocations familiales qu avec un salaire reduit

ou irrégulièrement perçu avec une indemnité journalière d importance variable s il est obligé d interrompre son travail

La prophylaxie des affections allergiques ne sera efficace que si le diagnostic en a ete *précoce* si pour l asthmatique par exemple les troubles respiratoires constatés ne sont encore que fonctionnels non compliqués de manifestations bronchitiques, d insuffisance respiratoire ou d emphysème pulmonaire Devenu un malade chronique, l asthmatique sera en effet arrete constamment dans son travail et finira son existence en infirme devenant une charge permanente pour sa famille et pour la Nation

Aussi est il souhaitable que les organismes responsables de la Sante Publique et de la Securite Sociale prennent toutes les mesures indispensables pour qu un asthme allergique au debut ou une dermatose professionnelle naissante puisse etre depisté de bonne heure

Toutes les maladies allergiques peuvent etre la cause d importantes repercussions economiques qui auront un retentissement aussi bien sur la *marche des entreprises que sur l équilibre* budgetaire

Les affections allergiques seront susceptibles d entrainer comme toutes les autres maladies sociales une réduction variable de la main d œuvre cause d une diminution notable de la production A l echelle nationale ce déficit de productivite pourra se faire lourdement sentir sur le budget général

Les soins medicaux et d hospitalisation la fourniture de medicaments toujours plus coûteux qu entraine le traitement des malades allergiques la frequence des assurances « Maladie » payees jusqu a six mois trois ans ou davantage et Invalidite » avec ses prestations en nature et une pension possible constituent de tres lourdes charges pour les Caisses de la Securité Sociale Elles pourraient etre notablement réduites (précocité de diagnostic prevention des maladies et soins particuliers donnés en temps voulu aux malades reconnus atteints d affections allergiques)

La lutte contre les maladies allergiques devrait etre organisee en France comme l est celle contre la tuberculose et le cancer Son rendement social serait profitable et rapidement acquis

Dans cette lutte le role du médecin est de premiere importance Aussi est il indispensable de former des medecins allergologues en leur donnant dans des centres specialisés la possibilite de s instruire sur les divers problemes cliniques thérapeutiques et médico sociaux que soulève l allergie Des medecins du travail des médecins d usine pourraient facilement acquerir dans ces centres les connaissances qui ne peuvent leur etre que fort utiles

Il est d une importance primordiale tant au point de vue social qu économique que les diverses manifestations cliniques reconnaissant l allergie comme cause soient précocement reconnues et traitées de façon efficace par des médecins compétents en allergologie

RÉSUMÉ

Ce sont surtout les manifestations allergiques d ordre respiratoire (asthme tracheo bronchique) et cutane (dermatoses réactionnelles) qui ont en France les plus importantes répercussions sociales et economiques

L asthme allergique doit etre reconnu et traite dès l enfance de façon a eviter son évolution vers l asthme allergique aggrave de l adulte

L asthme allergique de l adulte peut etre une maladie professionnelle il est dans ce cas plus individuel que collectif La frequence des dermites allergiques d origine professionnelle decoule surtout de l extension des industries chimiques

Les moyens de lutter contre l allergie professionnelle respiratoire ou cutanee resident dans le depistage la prevention la protection et le traitement de tous les troubles qu elle peut engendrer

Les charges que doivent supporter les organismes de Securite Sociale (frais medicaux et d hospitalisation cout elevé des médicaments prestations assurances « Maladie » et Invalidite) a propos de ces affections dont l origine allergique est trop souvent méconnue ou tardivement reconnue augmentent sans cesse Aussi est il indispensable qu un diagnostic precoce de la nature allergique de la maladie soit porte par un médecin competent en allergologie

Les maladies allergiques entrainent d importantes repercussions economiques dont le retentissement peut se faire sentir aussi bien sur la marche des entreprises (nombre croissant des jours d arret de travail) que sur l équilibre budgetaire general (pertes de salaire diminution de la productivité)

L attention des organismes responsables de la sante publique et de la Securite Sociale doit etre attiree sur l importance medico sociale des problemes que pose l allergie et leur retentissement sur l économie nationale

SUMMARY

In France allergic diseases both respiratory (tracheo bronchial asthma) and cutaneous (allergic dermatosis) are responsible for the more important hindrances imposed on economical and social life

Allergic asthma should be diagnosed and treated in childhood already in order to prevent its development to the severer allergic asthma of the adult age

Adult s allergic asthma is sometimes an occupational disease but in such cases rather belongs to the individual more than to the collective type

The frequency of occupational allergic dermatitis is mainly bound to the growth of chemical industries

Our weapons against occupational allergy are detection prevention protection and the treatment of all occasioned pathological disturbances

The financial burdens for the Health Service (medical and hospital costs expensive remedies allowances sickness and disability insurance) resulting from such diseases whose allergic origin is too often misjudged or belatedly recognized are steadily increasing

Therefore the early diagnose of a physician qualified in allergy is of absolute necessity

Allergic diseases involve important consequenc s they influence as well the life of business concerns (increasing number of lost working days) as the balance of the national budget (loss of loans reduction of productivity)

The attention of the Ministery of Public Health and of the Health service must be drawn on the medico social importance of allergic problems and their influence on national economy

ZUSAMMENFASSUNG

In Frankreich sind allergische Krankheiten sowohl des Respirationstraktes (Tracheobronchialasthma) als auch der Haut (allergische Dermatosen) fur d n bedeutendsten Schaden im okonomischen und sozialen Leben verantwortlich

Allergisches Asthma soll chon in der Kindheit diagnostiziert und behandelt werden um so die Entwicklung zur schwereren Form des allergischen Asthmas im Erwachsenenalter zu verhindern

Allergisches Asthma des Erwachsenen ist manchmal eine Berufserkrankung hangt in solchen Fallen aber mehr von d r Einzelperson als vom Kollektivtyp ab

Die Haufigkeit der beruflich bedingten alle gischen Dermatitis han t eng mit dem Anwachsen der chemischen Industrie zusammen

Unsere Waffen gegen die beruflichen Allergien sind Aufdeckung Vorbeugung Schutz und Behandlung aller beruflich verursachten pathologischen Veranderungen

Die fur das Gesundheitswesen (Arzt — und Krankenhauskosten ses te Medikamente Vergutungen Krankheits — und Invaliditatsversicherung) von solchen Krankheiten herruhrenden Finanzlasten von Krankheiten deren allergische Ursache so oft verkannt oder zu spat aufgedeckt wird sind standig im Ansteigen

Daher ist die Fruhdiagnose eines in Allergien bewanderten Arztes eine absolute Notwendigkeit

Allergische Krankheiten bringen bedeutende Konsequenzen mit sich sie beeinflussen sowohl die Arbeit von Industriekonzernen (anstei ende Zahl von verlorenen Arbeitstagen) als auch die Ausgeglichenheit des nationalen Budgets (Verlust von Darleben verminderte Produktion)

Die Aufmerksamkeit des Gesundheitsministeriums und d s Gesundheitswesens muss auf die medizinisch soziale Wichtigkeit allergischer Probleme und ihren Einfluss auf die Nationalokonomie gerichtet werden

RESUMEN

Son sobre todo las manifestaciones alergicas de orden respiratorio (asma traqueo bronquial) y cutaneo (dermatosis reaccionales) las que tienen mas repercusiones economicas y sociales en Francia

El asma alergico debe ser diagnosticado y tratado desde la infancia

a fin de evitar su evolución hacia el asma alergico agravado del adulto

El asma alergico del adulto puede ser una enfermedad profesional en este caso es más individual que colectivo La frecuencia de las dermitis alergicas de origen profesional se debe especialmente a la extension de la industria quimica

La manera de luchar contra la alergia profesional respiratoria o cutanea reside en el diagnóstico la prevencion la proteccion y el tratamiento de todos los trastornos que puede ocasionar

Los gastos que debe afrontar la *Securite Sociale* (honorarios medicos hospitalización costo elevado de los medicamentos prestamos seguros contra enfermedad e invalidez) como consecuencia de esas afecciones cuyo origen alergico es a menudo ignorado o reconocido tardiamente aumentan sin cesar Por lo tanto es indispensable que un diagnostico precoz de la enfermedad alérgica sea efectuado por un medico competente en alergología

Las repercusiones económicas de las enfermedades alergicas se hacen sentir de manera importante ya sea sobre el funcionamiento de las industrias (numero creciente de días de trabajo perdidos) ya sobre el equilibrio económico general (salarios disminución de la producción)

Debe llamarse la atencion a los organismos responsables de la *Santé Publique* y la *Securité Sociale* sobre la importancia medico social que presenta la alergia y sobre su influencia sobre la economia nacional

DENMARK

by

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TYPES AND INCIDENCE
ALLERGIC DISEASES PECULIAR TO DENMARK
OCCUPATIONAL ALLERGIC DISEASES

Approximately 1 p 100 of the Danish population is suffering from bronchial asthma to such a degree that the patients seek medical advice for the disease As to hay fever vasomotor rhinitis circumscribed œdema and allergic eczema the figures for each of these ailments are probably lower but no exact statement can be made because many of these patients—probably the majority—do not attend a doctor for their diseases but simply put up with them

No allergic disease is peculiar to Denmark but to our neighbour country Sweden birch hay fever is rather peculiar and the cause is that Sweden has plenty of birch trees The pollen season of birch in Sweden is the months of April and May

As occupational diseases vasomotor rhinitis and/or asthma due to flour in bakers and millers should be mentioned

CAUSES

Inhalants as the cause of bronchial asthma — The most common allergens as a cause of asthma in Denmark are house dust and feathers In comparison with other countries Denmark has a high incidence of asthma caused by feathers owing to the fact that practically everybody in this country sleeps with eiderdowns and featherpillows Among farmers allergy to animal hairs and feathers (poultry) is a frequent cause of asthma

Pollen asthma occurs in hay fever patients but only in the pollen season Outside the season pollen asthma is extremely rare On the other hand hay fever patients may become allergic to other allergens too e g house dust feathers etc and in such cases a perennial asthma will develop This happens in about 30 p 100 of hay fever patients if they are not hyposensi

tized In patients treated with specific hyposensitization a perennial asthm seldom develops

Fungi are not an infrequent cause of asthma in Denmark the most common fungi are hormodendrum *(cladosporium herbarum)* alternaria and aspergilli Among tomato gardeners *cladosporium fulvum* living on the leaves of tomatto plants may cause asthma

Inhalants as the cause of hay fever — The paramount cause of hay fever in Denmark is grass pollen about 90 p 100 of hay fever in this country is caused by grasses The pollinating season is from about June 1st to about July 20th About 5 p 100 of the hay fever patients complain of symptoms in April and May such complaints are due to tree pollen Another 5 p 100 have symptoms in July October (November) due to allergy to pollen of the compositæ Ragweed hay fever is extremely seldom In isolated areas ragweed can grow but it does not seem to spread

Inhalants as the cause of vasomotor rhinitis — It should be noticed that in vasomotor rhinitis inhalants seem to play a minor role in the etiology than in asthma and hay fever While in the two latter diseases inhalants act as causative agents in more than 80 p 100 inhalants can only be demonstrated as the cause of vasomotor rhinitis in about 45 p 100 The most common inhalants as a cause of vasomotor rhinitis are as in asthma house dust feathers and animal hair—and in bakers flour

FOODS

At present it is impossible to estimate the importance and the incidence food allergy It can be stated that in asthma food allergy is of very rare curence in vasomotor rhinitis food allergy may be of some importance d in circumscribed œdema allergy to foods is not infrequently the cause seems as if the usual daily foods such as rye wheat potatoes eggs and it relatively often can be the causes of vasomotor rhinitis and circum ibed œdema Definite figures cannot be given

ECTIONS

n approximately 40 p 100 the first onset of bronchial asthma develops onjunction with an infection of the upper respiratory tract and in many s particularly in early childhood the asthma attacks remain closely iected with catarrhal infections Very often the mother declares that e child is free from infections there is no asthma either This does not ssarily mean that infection is the cause of the child s asthma Gene an allergen such as house dust feather etc can be demonstrated as the cause but it means that the patient s condition is changing between a t and a manifest phase of allergy When there is no infection the nt can stand the allergens in question but when the mucous membranes e upper respiratory tract are vulnerable owing to the infection the y changes into a manifest phase and gives clinical symptom adults infections play a role too but not so markedly as in children

s

rt from asthma caused by acetylsalicylic preparations drugs are not an tant cause of asthma in nurses asthma may be seen as an occupational due to the handling of penicillin and streptomycin but on the whole

drugs only seldom cause asthma (still with the exception of acetylsalicylic preparations) In circumscribed oedema however drugs can rather often (in about 55 p 100) be demonstrated as causative agents

DIAGNOSIS

The most important way to the diagnosis is the taking of a detailed history Many other diagnostic procedures can be omitted if the doctor takes the necessary time for a good anamnesis

Skin tests The discussion of whether scratch or intradermal tests should be applied is outside the scope of the present paper Both methods give good results when correctly interpreted and both methods have both advantages and disadvantages The author uses intradermal tests and at the first consultation the patient is tested with about 30 allergens each in a concentration of 1 1 000 (with some allergens e g egg and if there is a suspicion of pronounced sensitivity weaker concentrations are applied)

At the next consultation the patient will be tested with those allergens to which he reacted positively at the first examination but now in different dilutions of the allergens concerned generally with the following concentrations 1 10 000 000—1 1 000 000—1 100 000—1 10 000—1 1 000—and may be 1 100 If the patient reacted strongly to 1 1 000 the test with 1 100 should be omitted This allergometrical titration is made in order to find the proper concentration for the initial dose of the treatment If the patient is reacting negatively to 1 10 000 000 but positively to 1 1 000 000 and increasingly positively to the stronger dilutions specific hyposensitization should be commenced with the 1 1 000 000 dilution

PREPARATION OF EXTRACTS

Table I gives the necessary details

DELAYED REACTIONS

Delayed reactions to allergens which generally give immediate reactions only are not considered important in the diagnosis of asthma

FOOD TESTS

In cases of vasomotor rhinitis and circumscribed oedema testing with food allergens may give valuable help but it cannot be denied that disappointments may be met with The foods that generally give reliable results are cereals potatoes fish coffee and shellfish Less reliable are apparently the results of testing with milk meat fruits vegetables and spices As always in allergologic diagnostic procedures the results of skin testing must be correlated with the patient s history and trial diets should be prepared When a diagnosis is uncertain the patient should be put on a diet consisting of the foods to which he reacts negatively and which he knows that he can tolerate When the patient has become symptomfree on such a diet another food is added to it and the patient is kept under observation for the following 48 hours If no symptoms occur still another food is added to the diet a new observation for 48 hours follows and so forth

TESTS WITH BACTERIAL EXTRACTS

In cases suspicious of bacterial allergy skin tests with bacterial extracts are performed The results are checked both after 15 minutes and after

TABLE 1 — *Preparation of Allergens*

	PURIFIED HOUSE DUST	DUST FROM PAT.'s home	ANIMAL HAIRS	FEATHERS	MEAT FISH	VEGETABLES	FRUITS	SEEDS NUTS	CEREALS	MILK (cream removed)	EGGS	POLLENS	MOULDS	TOBACCO
grinding					+	+	+	+	+					
squeezing						+	+							
sifting	+											+		
extraction with ether	+				+			+						
extraction with distilled water	+				+	+	+	+	+		+			
extraction with 14 p 100 alcohol			+	+										
vacuum distillation			partly	+										
precipitation with acetone			+		+	+	+	+	+	+	+			
do double fractioned	+													
paper filtration			+		+	+	+	+	+	+	+			
washing with ether				+						+	+			+
cultivation													+	
washing with alcohol													+	+
drying			+	+	+	+	+	+	+	+	+	+	+	+
pulverizing			+	+	+	+	+	+	+	+	+		+	
extract on with buffer solution	+	+	+	+	+	+	+	+	+	+	+	+	+	+
pape filtration	+	+	+	+										
dialysis	+											+		

24 hours The evaluation is difficult a positive reaction only indicates that the patient has had an infection with the bacteria concerned but says nothing about the possible relationship between the bacterial infection and the patient s asthma

OTHER DIAGNOSTIC TESTS

1 Provocation tests with an aerosol of the antigen in question are performed in cases where the diagnosis is not clear For provocation a 1 100 concentration of the antigen is used the vaporation being performed by a pancompressor The patient must be in a symptomfree period during the experiment he must be under constant observation and stethoscopy of his lungs is done every second minute As soon as rhonchi and or rales appear or an asthma attack is beginning the experiment must be interrupted If nothing has happened after 15 minutes the experiment is discontinued and the result is interpreted as negative

2 In cases off scientific interest the passive transfer a m Prausnitz Kustner is performed

THERAPY

Specific hyposensitization is used in cases where the specific inhalants can not be completely eliminated In asthma hypo ensitization with extracts of house-dust feathers fungi animal hairs flour etc is continued as a long term treatment for several years When the treatment has reached the so called maximum do e generally 1 100 0 7 ml a continuation course of this dose is given once every 2nd 3rd 4th week during the next year To discontinue the treatment two things are required 1° the patient must have been asthma free for at least a year 2° the intradermal reactions to the allergen(s) in question must be definitely weaker than before hyposensitization was instituted

In hay fever patients pre seasonal hyposensitization is preferred Usually the patients get inoculations from March to June This is done for at least three seasons the fourth year hyposensitization can be tentatively omitted if the intradermal reactions to pollens have decreased Generally treatment is given again in the fifth year and so on every second year

PROFESSIONAL AND EDUCATIONAL

Number of physicians in Denmark specializing in allergy

Full time rather few scarcely more than 10
Part time approximately 50

Allergy Societies

1 Society The Danish Society for Allergological Research
Number of members about 50 active members
Activity at least four meetings yearly

Teaching of allergy

Besides teaching by the university professors in internal medicine paediatrics dermatology and otorhinolaryngology both undergraduate and post graduate education in allergy is being given at the two Allergy Clinics of the University (one clinic for paediatric allergy and one for allergy in adults)

Requirements for specialization

At present allergy is a subspecialty of internal medicine This means that a specialty in internal medicine is required first and after some years work in an Allergy Clinic specialization in allergy can be obtained It is probable that in a rather near future specialization in allergy will be recognized also as a subspecialty of pædiatrics and dermatology A committee is working with this problem

SUMMARY

Approximately 1 p 100 of the Danish population is suffering from bronchial asthma to such a degree that the patients seek medical advice for the disease

Inhalants The most common causes of bronchial asthma in Denmark are house dust and feathers Among farmers animal hairs and feathers (poultry) are frequent causes of asthma

The paramount cause of hay fever in Denmark is grass pollen Only about 10 p 100 is caused by pollens from trees or compositæ Ragweed hay fever is extremely seldom

While in asthma and hay fever inhalants act as causative agents in more than 80 p 100 (in hay fever probably in 100 p 100) inhalants can only be demonstrated as the cause of vasomotor rhinitis in about 45 p 100

Foods act as *relatively* frequent causes of circumscribed œdema and urticaria

Drugs Apart from asthma caused by acetylsalicylic preparations drugs are not a frequent cause of asthma In circumscribed œdema however drugs play an important role as causative agents

Skin tests give valuable help in the diagnosis of allergic diseases caused by inhalants In food allergy skin tests may be helpful in drug allergy and in bacterial allergy they are generally without value

Specific hyposensitization is used in cases where the specific inhalants cannot be completely eliminated In some cases of drug allergy (insulin penicillin streptomycin) hyposensitization can be useful too and in cases of food allergy oral hyposensitization may give good results

RÉSUMÉ

1 p 100 environ de la population danoise est atteinte d asthme assez sérieux pour rendre des soins médicaux nécessaires

Pneumallergenes Au Danemark les causes d asthme bronchique les plus frequentes ont la pou siere domestique et les plumes Parmi les agriculteurs les poils d animaux et les plumes des volailles sont souvent responsables de l asthme

La cause dominante du rhume des foins au Danemark est le pollen des graminées 10 p 100 seulement des cas d asthme sont imputables aux pollens des arbres et des composées

Le rhume des foins occasionné par l'Ambrosia est extrêmement rare

Alors que les allergènes atmosphériques sont la cause de plus de 80 p 100 des cas d'asthme et de rhume des foins (vraisemblablement 100 p 100 pour le rhume des foins) on ne peut prouver leur action pathogénique que pour 45 p 100 environ des cas de rhinite vasomotrice

Les allergènes alimentaires Les aliments sont les causes *relativement* fréquentes d'œdème de Quincke et d'urticaire

Allergène médicamenteux En dehors de l'asthme imputable aux préparations à base d'acide acetyl salicylique les médicaments sont des causes d'asthme rares Dans le cas de l'œdème de Quincke cependant les médicaments peuvent souvent être sérieusement incriminés

Tests cutanés Les tests cutanés sont des éléments de valeur pour le diagnostic des allergies par allergènes respiratoires Ils peuvent rendre des services dans le cas d'allergies alimentaires et sont en général sans signification pour les allergies médicamenteuses ou microbiennes

Désensibilisation spécifique Il est fait appel à ce mode de traitement dans les cas où les allergènes spécifiques atmosphériques ne peuvent être complètement éliminés Dans certains cas d'allergie médicamenteuse (insuline pénicilline streptomycine) la désensibilisation peut être utile La désensibilisation par voie buccale peut donner de bons résultats pour les allergies alimentaires

ZUSAMMENFASSUNG

Ungefahr ein Prozent der danischen Bevolkerung hat doch so schwere Asthmaanfalle dass arztliche Behandlung notwendig ist

Luftallergene In Danemark sind der hausliche Staub und Federn der haufigste Grund des Asthma bronchiale Bei den Landwirten sind Tierhaare und Geflugelfedern haufig fur Asthma verantwortlich zu machen

In Danemark ist die wichtigste Ursache fur Heuschnupfen in den Graserpollen zu sehen 10 p 100 der Asthmafalle werden durch Baumbluten und Compositaen hervorgerufen

Der durch Ambrosia hervorgerufene Heuschnupfen ist sehr selten

Wahrend Luftallergene fur mehr als 80 p 100 der Asthma und Heuschnupfenfalle verantwortlich sind (wahrscheinlich 100 p 100 fur den Heuschnupfen) kann man ihre pathogene Wirkung nur bei cirka 45 p 100 der Falle von Rhinitis vasomotorica beweisen

Nahrungsmittel Die Nahrungsmittel sind *relativ* haufig die Ursache von umschriebenen Ödemen und Urtikarien

Medikamente Sieht man von den Asthmafallen ab die durch Praparate mit einer Acetyl Salicylsauere Grundlage verursacht werden sind die Medikamente nur selten die Ursache fur Asthma Fur Falle von umschriebenen Ödemen hingegen konnen Medikamente oft ernstlich verantwortlich gemacht werden

Kutanteste Die Hautteste sind wertvoll fur die Diagnostik von durch eingeatmete Allergene bedingten Allergien Sie konnen fur die Falle von Lebensmittelallergien von Bedeutung sein sind im allgemeinen ohne Bedeutung fur medikamentose und bakterielle Allergien

Spezifische Desensibilisierung Man soll sich an diese Behandlungsmoglichkeit in jenen Fallen erinnern in denen die Luftallergene nicht vollstandig

ausgeschaltet werden konnen Bei gewissen Fallen einer medikamentosen Allergie (Insulin, Penicillin Streptomycin) kann die Desensibilisierung von Nutzen sein Die Desensibilisierung *per os* kann bei Lebensmittel allergien gute Resultate zeigen

RESUMEN

Aproximadamente el 1 p 100 de la poblacion danesa sufre asma bronquial de una intensidad tal que los pacientes solicitan atención médica para su enfermedad

Inhalantes Los causantes más frecuentes de asma bronquial en Dinamarca son el polvo doméstico y las plumas Entre los granjeros los pelos de los animales y las plumas de gallina son causas frecuentes de asma

El agente causal de polinosis de mayor importancia es el polen de gramineas Solamente el 10 p 100 de las polinosis es debida a polen de árboles o compuestas Los casos de alergia por «ragweed» son extremadamente raros

Mientras que en el asma y la polinosis los inhalantes actuan como agentes etiológicos en el 80 p 100 de los casos (en la polinosis tal vez en el 100 p 100), solamente pueden ser demostrados en el 45 p 100 de los casos de rinitis vasomotora

Los *alimentos* son causas *relativamente* frecuentes en el edema y urticaria

Drogas Aparte de los casos provocados por el ácido acetilsalicilico las drogas no son causas frecuentes de asma pero desempenan un papel importante en el edema

Los *tests cutaneos* son de valor en el diagnóstico de las enfermedades alergicas provocadas por inhalantes En los casos de alergia alimenticia pueden ser de ayuda y en los casos de alergia a drogas o alergia bacteriana son por lo general sin valor

La *hiposensibilizacion específica* se utiliza en los casos en que los inhalantes responsables no pueden ser completamente eliminados Puede ser tambien util en algunos casos de alergia a drogas (insulina estreptomicina penicilina) La desensibilización por via bucal puede dar buenos resultados en la alergia alimenticia

SWEDEN

by

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Asthma one of the principal allergic complaints in internal medicine is common in Sweden with an incidence of about one per cent although no reliable figures are available The disease occurs in all parts of the country but cert in low lying humid tracts which are more common in the south show higher figures than the hilly regions of the north Of all allergic diseases asthma is the most important from the social aspect

Hay fever occurs in Sweden in three seasons From March to May the condition is due to tree pollen and especially that of the silver birch in June and July grass pollen is the prime factor and in late summer it is various types of Compositæ and principally the ox eye daisy Between these seasons there may be hypersensitiveness to other plants such as rape The flowering time varies widely from one part of the country to another owing to the large difference in latitude

In Sweden pollen allergy is generally treated by hyposensitization If this is not effective antihistamines are given ACTH and steroids are used only in exceptional cases

Gastro intestinal allergy due to food sensitization appears to be rather uncommon in Sweden though opinions on this are divergent (1)

As early as 1937 eosinophilic infiltrates were detected in the gastro intestinal tract Isolated cases of such infiltrates in the stomach have been found which bear some resemblance to cancer However eosinophilia in the gastric mucuous membrane may also occur in cancer of the stomach (2)

In Sweden the summer is short while the autumn and winter are long and during the cold season the people spend most of their time indoors The dwellings are generally good but small a factor that favours the spread of infections of the respiratory tract and the contraction of dust allergy

From recent work it is evident that in Sweden infections both bacterial and virus constitute a major factor in the onset of asthma some 60 per 100 of the cases of endogenous asthma and 40 p 100 of those of exogenous asthma having their first attack in connection with an infection of this type (3)

Some patients are sensitive to dust but rarely experience distress other than that due to infections In such cases hyposensitization therapy with dust extracts seems indicated in order to eliminate as far as possible the chronic irritation of the bronchi arising through the dust sensitization Resistance to infection may thus be increased

There are three factors of special importance in the long term treatment of asthma specific hypersensitiveness general infections particularly of the respiratory tract and focal infections

It is important to bear in mind when evaluating the results of asthma treatment that in the individual case the condition is often due to a complex of factors and that the success of the therapy will depend on how effectively the principal ones can be eliminated The value of hyposensitization would seem to be indisputable in cases where the major factors are specific The poor results occasionally obtained with this treatment do not necessarily imply failure of the method The specific factor may be eliminated but its importance may have been small compared with other factors. The successful treatment of asthma depends on the detection and elimination or treatment of as many ætiologic factors as possible and especially the most significant ones

In Sweden specific hyposensitization is indicated in about 20 per 100 of the cases of asthma

Focal infections are often the cause of the initial attack of various allergic conditions and in asthma it is infections of the paranasal sinuses that are primarily responsible (4) Apical granuloma may be the causative factor in both asthma and urticaria

Since the beginning of the nineteen thirties there has been a great interest in both manifest and latent allergy (5) Tuft an American specialist in this field uses the terms clinical and non clinical allergy for the manifest and latent forms The term latent allergy means that the condition is characterized by a skin allergy that is of no clinical significance and does not imply the presence of a disease

Skin reactions with no clinical significance are quite common especially in certain trades Exposure and provocation tests can be used to show whether a positive skin reaction reflects a manifest or a latent allergy Moreover they may disclose whether there is a manifest allergy when the skin reaction is negative

Provocation tests are performed by inhalation of various antigen solutions with the aid of a suitable spray In general rising concentrations are used the strongest being 1 10 One millilitre of each concentration is usually inhaled with an interval of five to ten minutes between each inhalation (6 7 8)

The provocation test is fully reliable only for patients who are subjectively symptom free On the other hand it is of no consequence whether the breathing sound is quite normal before the test is begun except that where it is not it will be more difficult to judge the results of the test If the breathing sound is normal both before and after the inhalation of the solution but is asthmatic after inhalation of antigen of a certain strength there is no doubt that the antigen in question can give rise to asthma An objective record of the asthma is then no more necessary than it is for reaching a diagnosis of asthma On the other hand in cases where prior to the provo-

cation test there was disturbed breathing it may be difficult to decide whether it is worse after inhalation of the antigen An objective record of one of the respiratory functions before and during the course of the test may then prove an invaluable aid Various methods have been used to this end such as measurement of the vital capacity pneumometry recording of the oxygen saturation of the arterial blood the intrapulmonary mixing of the respiratory gases and the compliance Of these methods the determination of the vital capacity and pneumometry are easy to perform but the values obtained are highly dependent on the cooperation of the patient If the patient is apprehensive or tired the values may be affected There is no reduction in the oxygen saturation in the mildest forms of asthma so that this method is not sufficiently sensitive for use as an objective provocation test Determination of the intrapulmonary mixing and measurement of compliance are two methods that are less dependent on the co operation of the patient the former of them probably being the more sensitive

The results of provocation tests with inhalation allergens would seem to differ from one part of the world to another In Sweden cases of asthma who gave a positive skin reaction and who were subjected to provocation tests with inhalation allergen gave a positive response in 72 p 100 of the cases for house dust 59 p 100 for pollen and 20 p 100 with animal epithelium A positive skin reaction to dust is thus of much greater value as a sign of a hypersensitiveness of significance for the patient s disease than is a positive reaction to animal epithelium Pollen holds an intermediate position

In a particular study when the skin reaction was negative provocation tests with inhalation allergen gave asthma symptoms in 16 p 100 of the cases Among the antigens that in spite of negative skin reactions elicited a positive response to the provocation tests in cases of asthma were animal epithelium dust pollen and mould spores

The purpose of the provocation test is to obtain a clear indication of whether or not specific treatment should be given The most reliable indication for specific hyposensitization therapy is probably a positive provocation test Such tests are admittedly time consuming but they are in many cases an indispensable means of deciding whether the still more lengthy hyposensitization therapy should be proceeded with In some cases however a case history and skin tests may be decisive so that the provocation test need not be performed

Another problem that has awakened great interest in Sweden is the incidence of bronchial infection of bacterial origin in cases of asthma (9) Studies have shown that the sputum may be thick and yellow without there being an infection Cytologic examination of such sputum may reveal only eosinophil leukocytes It is usually impossible to decide from the macroscopic appearance of the sputum whether there is a bacterial bronchial infection or not Bronchial secretion obtained by normal bronchoscopy cannot be used for cultures as it is often contaminated by infection from the throat On the other hand by introducing a tracheal tube through which a catheter is passed contamination is avoided Moreover owing to the slight curvature of the tube the narrow catheter will stay in the centre on its passage through the tracheal tube and will therefore not touch the rim of the lower orifice which may be contaminated on passage

through the larynx The tracheal secretion obtained in this way, if necessary after irrigation with saline is sterile in at least 90 p 100 of the cases It is just as frequently sterile in asthma cases with no increase in the erythrocyte sedimentation rate Asthma patients with an elevated ESR present bronchial infection more often than healthy persons the bacteria found being chiefly Hæmophilus influenzæ and pneumococci—that is to say the same bacteria as were found by Mulder in his studies on washed sputum In the study of chronic bronchitis English workers have recently reached similar results by different methods (10) They too found sterile conditions in the bronchial tract of healthy persons

Not only the ESR but also the leukocytes in the sputum and bronchial secretion may be of value in deciding whether or not there is bacterial infection of the bronchi In this case a greater or lesser number of neutrophil leukocytes may be found If there is a marked preponderance of eosinophil leukocytes together with a much elevated ESR some other disease than asthma may be suspected—Loffler s syndrome for instance (IOB)

If there are no definite signs of infection in asthma antibiotics are best avoided Where there is a high temperature this therapy should we feel *be postponed a day or two*

Another problem that has received much attention in Sweden is the pathophysiology of asthma especially the changes incurred in the respiratory gas exchange (11) In severe asthma pulmonary ventilation and oxygen uptake are not commensurate with the actual needs of the body During the most severe attacks both in man and in animal the ventilation of the lungs and the uptake of oxygen are lower than under basal conditions This leads to an oxygen deficit during attacks a deficit that must be made good afterwards The alteration in gaseous tension during asthma attacks provokes changes in tissue respiration due in part to destruction of co-enzymes This suggests the possibility of an altered tissue respiration in man too that may be of clinical importance

Important investigations on the pathology of experimental asthma have been performed (11 B)

With the recent gain in the popularity of steroid therapy in cases of asthma the question has arisen as to whether and to what extent atrophy of the suprarenals may result from this treatment To some degree ACTH has been given at intervals of one to three weeks in order to reduce the risk of these atrophic changes The problem is still not solved however but the work is continuing In this connection one may well heed the American findings since the introduction of steroid theraphy the morbidity of asthma has declined—but not the mortality (12)

In Sweden observations have been made on allergic reactions to ACTH (13) In most cases they were mild but a few were severe the strongest occurring when ACTH was injected intravenously

Experiments on the cat have shown that ACTH and histamine have a different effect on the number of thrombocytes in the peripheral blood (14)

Anaphylactic reactions and some allergic states are accompanied by *thrombocytopænia this is so marked an effect that it can be used as a* diagnostic aid It has been shown that the thyroid hormone seems to influence the antigen antibody reaction and perhaps also the target organs of this reaction (15)

A factor that is of interest in the allergic reaction is the increased proteolytic activity that can be demonstrated in extracts of shock organs. Eosinophil leukocytes show no proteolytic activity in the presence of specific antigen (16).

The number of asthmatic children in Sweden has increased during the last few decades until today there are about 10 000 in the schools (the total population of Sweden is about 7 millions) (17). In the elementary schools of Stockholm the incidence is about 1.4 p. 100. For those children who resist all therapy special homes are recommended. A boarding school for about 20 asthmatic children has existed in Stockholm since 1936. The children live there during the school terms but in the summer they usually stay at home or live at summer colonies together with other children. In 1955 the Swedish Red Cross started another school home for asthmatic children. An asthma home should be located in the neigbourhood of a large town or in the centre of a country in view of the desirability for collaboration with pædiatric hospitals. It is not necessary for such homes to b at a high altitude. A specialized nursing personnel is an advantage. The children can often attend a nearby school.

In an investigation on the specific treatment of children it was stressed that many positive skin reactions are of no clinical significance (18).

Other studies have shown that auto vaccine therapy in intrinsic asthma is not entirely a non specific protein treatment. There is some degree of specificity for staphylococci. Staphylococcus vaccine has been found to give better results than polyvalent vaccine containing no staphylococci (19).

Studies with the radio active phosphorus P^{32} have shown that the absorption is more rapid if the skin is œdematous. The shorter disappearance time for intradermally injected agent is not attributable to a change in the reactivity of the tissues. It was shown that compression of the œdematous skin around the site of injection resulted in more marked reaction (20).

Chronic local anaphylactic reactions could be produced in rabbit skin with a relatively pure antigen (bovine serum albumin). [illegible] developed at the site of the antigen [illegible] of cortisone at the he[illegible] in a distinct reductio[illegible]

The presence in the [illegible] sarcoidosis cases of a factor (anticutins) that influences the tuberculin reaction could not be demonstrated in carefully performed investigations in 1956. It was however shown that the degree of the tuberculin serum reaction at 48 hours is correlated to the response to the mixture at 15 minutes and to the tuberculin control at 48 hours (22).

Allergic otitis has been closely studied and has been found to be more common than has previously been thought. Smear examinations of the purulent discharge can yield valuab e information if an infection exists or the disease has an allergic origin (23).

Extensive studies have been performed on occupational diseases of allergic origin (24, 25).

In recent years there have in Sweden been various opinions on the position of allergy. The dermatologists have maintained that in order to work with allergy one should be a dermatologist (26). It has been maintained that good training as a dermatologist is necessary for being able to perform

research in clinical experimental allergy In 1955 the Chair in Clinical Experimental Allergy was given to a dermatologist However owing to opposition the title of the Chair has since been changed to Dermatologic Allergy This is the reason why Sweden s only Chair concerned with allergy is in Dermatologic Allergy The opinion is gaining ground that a medical man cannot deal with all allergic complaints It would seem most appropriate that each specialist field should be concerned with its own allergic complaints Internists would thus be concerned primarily with allergy in internal medicine dermatologists with allergic conditions of the skin and so forth Of course an intimate co operation is highly desirable in the treatment of several allergic diseases Thus it is often necessary for an internist who is specialized in allergy and who is treating a case of asthma to collaborate closely with an otolaryngologist interested in allergy problems as it is often impossible to clear up the asthma until the nose and parasinuses are in order On the other hand it would seem to be unreasonable that a dermatologist with no real training in internal medicine should deal with asthma cases where the most difficult problem is often centred on functional changes in the heart and lungs It might therefore be looked upon as a gratifying development that lung specialists who formerly were engaged mainly with tuberculosis have in recent years taken up allergy and received training in the subject—provided of course that the lung specialists have a thorough grounding in internal medicine One reason for this development is that the number of tuberculosis patients has fallen appreciably in recent years as a result some sanatoria with suitable accommodation have begun to treat asthma cases

Allergy specialists belong to a variety of fields That opinions should differ among them is therefore hardly to be wondered at This difference may however lead to an undesirable development of the science of allergy in a particular country One might state without exaggeration that internal medicine should always assume a central position in the science of allergy There is at present one Assistant Professor of Internal Allergy and one in Dermatologic Allergy Moreover there are departments primarily for allergic complaints in Stockholm and Gothenburg

The Board of Pensions has special hospitals for rheumatic and asthmatic patients these are situated in both high and low lying country

Short courses in allergy are given in Stockholm and Gothenburg In other University towns instruction is given in allergy in association with internal medicine dermatology and otolaryngologic diseases At most hospitals there are facilities for allergy examinations In September the Scandinavian Society for Allergy Research will hold a 4 day post-graduate course in allergy in Gothenburg with lecturers from all the Scandinavian countries This is the first course of this type

SUMMARY

Asthma is the allergic complaint of the greatest social significance Hay fever occurs in Sweden in three seasons In the spring the complaint is due to tree pollen especially that of the silver birch in the height of summer grass pollen is responsible and in late summer various types of Compositæ The incidence of food sensitization in adults appears to be lower although opinions differ on this point Among children asthma is common

In Sweden the summer is short and the autumn and winter long and during the cold seasons the population spend most of their time indoors The dwellings are generally good but small especially in the towns a factor of some significance in the contraction of infections of the respiratory tract and dust allergy

Certain aspects of allergy have received much attention in Sweden among them the importance of the provocation test in the ætiologic study of allergic diseases the occurrence of respiratory tract infections occupational diseases of an allergic type the importance of endocrinic factors the thrombocyte account steroid therapy and associated risks in the form of impairment of the suprarenals

In Sweden there is at present one Chair in dermatologic allergy and one Assistant Professorship in each of internal allergy and dermatologic allergy In recent years there have been divergent opinions on which of the fields allergy really belongs but it is now I think being realized that each field should be responsible for its own allergic complaints although close collaboration between the various specialists is often necessary It is becoming increasingly evident that internal medicine must always assume a central place in the science of allergy

There are departments primarily for allergic complaints in Stockholm and Gothenburg The Board of Pensions has special hospitals for rheumatic and asthmatic patients these are situated in both high and low lying country There are special homes for children with severe asthma

Short courses on allergy are given in Stockholm and Gothenburg In other University towns instruction is given in allergy in association with internal medicine dermatology and otolaryngologic diseases At most hosp[illegible] xaminations In September 1958 the [illegible] esearch will hold a 4 day post grad[illegible] with lecturers from all the scandinavian countries This is the first course of this type

RÉSUMÉ

Parmi les maladies allergiques l asthme est celle dont les incidences sociales sont les plus importantes Le rhume des foins apparait en Suede au cours de trois saisons au printemps la maladie est provoquée par le pollen des arbres principalement les bouleaux au milieu de l été ce sont les pollens des graminées qui sont a incriminer et a la fin de l été differentes variétés de composées L allergie alimentaire est plus rare bien que sur ce sujet les opinions varient L asthme est commun chez les enfant.

En Suede les étés sont courts et les hivers et les automnes longs pendant la saison froide la population passe la majeure partie de son temps a l interieur des maisons Les lieux d habitation sont en general satisfaisants mais dans les villes surtout petits on peut voir la une raison pour leurs occupants de contracter plus facilement des infections de l appareil respiratoire et l asthme du aux poussieres domestiques

Certains aspects de l allergie ont ete particulierement etudies en Suede parmi eux le test de provocation dans l étude étiologique des maladies allergiques les manifestations d infection des voies respiratoires les maladies professionnelles allergiques les facteurs endocriniens la numeration des thrombocytes les traitements par les steroides et le risque d atteintes surrenaliennes qu ils peuvent occasionner

Il existe en Suede une chaire de dermatologie allergique et deux chaires de professeurs charges de cours pour l allergie interne et l allergie dermatologique

Au cours des dernieres années les opinions varient quant au domaine medical dans lequel l allergie devait etre classee aujourd hui bien qu une étroite collaboration entre les divers spécialistes soit souvent nécessaire on conçoit que chaque branche de la médecine doit etre responsable des maladies allergiques dependant de son activite

Il devient de plus en plus evident que la place principale dans la science allergologique doit etre tenue par la médecine interne

Il existe a Stockholm et a Gothenburg des services médicaux traitant principalement les maladies allergiques

Le Ministere des Pensions a des hopitaux speciaux pour les rhumatisants et les asthmatiques situes a basses ou hautes altitudes Il existe des homes médicaux spéciaux pour les enfants atteints d asthme grave

L enseignement allergique est donné a Stockholm et a Gothenburg dans des cours de courte duree Dans les autres villes universitaires l instruction allergique est jointe aux leçons de médecine interne de dermatologie et d oto rhino laryngologie

Les examens allergologiques peuvent etre pratiqués dans presque tous les hopitaux

En 1958 la Societe scandinave pour la recherche allergologique organise un cours d allergie post scolaire d une duree de quatre jours a Gothenburg des leçons seront données par des professeurs venant de tous les pays scandinaves C est la premiere fois qu une reunion de ce genre est organisée

ZUSAMMENFASSUNG

Unter den allergischen Krankheiten ubt Asthma den wichtigsten Einfluss auf das soziale Leben aus, der Heuschnupfen tritt in Schweden im Verlaufe von 3 Saisonen auf im Fruhling wird die Krankheit durch Baumblüten besonders der Birken hervorgerufen in der Mitte des Sommers sind es die Graspollen und am Ende des Sommers verschiedene Arten der Compositae

Die durch Nahrungsmittel hervorgerufene Allergie ist viel seltener obwohl hier die Meinungen noch auseinandergehen Das Auftreten des Asthmas bei Kindern ist gelaufig

In Schweden sind die Sommer kurz und die Winter- und Herbstjahreszeiten lang während der kalten Jahreszeit verbringt die Bevölkerung die meiste Zeit im Inneren der Häuser Die Wohnmöglichkeiten sind im allgemeinen zufriedenstellend aber besonders in den Städten klein man kann darin einen Grund sehen dass die Besitzer leichter an durch Infektionen der Atemwege und häuslichen Staub bedingtes Asthma erkranken

Verschiedene Merkmale von Allergien wurden in Schweden gründlich studiert unter ihnen der Provokationstest zum Ätiologiestudium allergischer Krankheiten die Infektionsmanifestationen der Atemwege die allergischen Berufserkrankungen die endokrinen Faktoren das Zählen der Thrombozyten die Behandlung mit Stereoiden und die Gefahr von Schäden die durch die Nebenniere hervorgerufen werden können

Es bestehen in Schweden ein Lehrstuhl für allergische Dermatologie und 2 Lehrstühle für ausserordentliche Professoren für Allergie in der Inneren Medizin und in der Dermatologie

Im Verlaufe der letzten Jahre wechselte die Auffassung in welches medizinische Gebiet Allergie eingestuft werden soll heutzutage obschon eine enge Zusammenarbeit der verschiedenen Spezialisten oft notwendig ist nimmt man an dass jede Branche der Medizin je nach ihrer Tätigkeit für allergische Krankheiten zuständig ist Grundsätzlich soll der erste Platz in der Allergieforschung von der Inneren Medizin eingenommen werden

In Stockholm und Gothenburg bestehen medizinische Abteilungen die auf die Behandlung allergischer Krankheiten spezialisiert sind

Das Pensionsministerium besitzt Krankenhäuser sowohl in grosser als auch niederer Höhenlage speziell für Rheumatiker und Asthmatiker Es gibt spezielle Heime für Kinder die an schwerem Asthma leiden

In Stockholm und in Gothenburg wird in kurzdauernden Kursen Unterricht in Allergie gegeben In den anderen Universitätsstädten ist die Ausbildung in Allergie an die Vorlesungen über Innere Medizin gebunden auch an denen über Dermatologie und HNO

Untersuchungen hinsichtlich der Allergie können in fast allen Krankenhäusern durchgeführt werden

1958 veranstaltet die skandinavische Gesellschaft für Allergieforschung einen viertägigen Allergiekursus in Gothenburg die Vorlesungen werden von Professoren aus allen Ländern Skandinaviens gehalten Es ist das erste Mal dass eine Versammlung dieser Art organisiert wurde

RESUMEN

El asma es la enfermedad alérgica de mayor significación social La polinosis en Suecia se presenta en tres estaciones en la primavera debida al polen de árboles especialmente álamo plateado en pleno verano por el polen de gramíneas y hacia el fin del verano por varios tipos de compuestas La incidencia de la sensibilización alimenticia en los adultos parece ser menor aunque sobre este punto las opiniones difieren Entre los niños el asma es frecuente

En Suecia el verano es corto y el otoño e invierno largos Durante las estaciones frías la población pasa la mayor parte de su tiempo en el interior

de las casas que aunque confortables son pequenas, especialmente en los *pueblos chicos* es este un factor de cierta importancia en el contagio de las infecciones del árbol respiratorio y en la alergia al polvo doméstico

Algunos aspectos de la alergia han recibido mucha atención en Suecia Entre ellos la importancia de los *tests* de provocación en el diagnóstico etiológico la existencia de infecciones del arbol respiratorio las enfermedades ocupacionales alergicas la importancia de los factores endocrinos el recuento de trombocitos la terapeutica con esteroides y sus riesgos debidos a trastornos de las suprarrenales

Actualmente hay en Suecia una Cátedra de Alergia Dermatològica y dos Profesores Asistentes de Alergia Interna y Alergia Dermatológica En los ultimos años ha habido una serie de controversias sobre a cual rama la alergia realmente pertenece pero en la actualidad parece haberse reconocido que cada rama de la medicina tiene sus propios trastornos alergicos lo cual hace necesaria la colaboración entre los correspondientes especialistas Cada vez se hace más evidente el papel fundamental de la medicina interna en la ciencia alérgica

Hay institutiones dedicadas especialmente a la atención de enfermos alergicos en Estocolmo y Gotenburgo El *Board of Pensions* posee espaciosos hospitales para pacientes reumáticos y asmáticos, situados tanto en las zonas altas como bajas del país Hay establecimientos especiales para niños con asma grave

En Estocolmo y Gotenburgo se dictan cursos breves sobre alergia y en otras universidades la enseñanza alérgica se da junto con las de medicina internas dermatología y otorrinolaringología En la mayoría de los hospitales hay comodidades para los exámenes alergicos La Sociedad Escandinava para las Investigaciones Alérgicas realizará un curso de 4 días para postgraduados sobre alergia en la ciudad de Gotenburgo en el que participarán conferenciantes de todos los países escandinavos Es el primer curso de ese tipo que tiene lugar

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MEXICO

por

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CARACTERISTICAS GEOGRAFICAS Y METEOROLOGICAS

SITUACION La Republica Mexicana con una extensión de 2 000 000 de km² tiene la figura de un cuerno de la abundancia estando limitada al norte por los Estados Unidos de Norte America al sur la Republica de Guatemala y las Honduras Británicas al este por el Golfo de Mexico y el Mar Caribe y al oeste por el Oceano Pacífico Extendiendose desde los 14° hasta los 32° latitud Norte se encuentra atravesada por el trópico de Cáncer la parte sur está dentro de la zona tropical y tiene dos veces al año el sol sobre su zénit La parte norte que es la más grande se extiende en la región extratropical llegándole los rayos solares inclinados segun angulos variables

CLIMATOLOGIA La complicada orografia de la Republica Mexicana impide hacer generalizaciones no hay grandes superficies que disfruten de tipo de clima determinado porque la altitud variable en áreas cortas provoca modificaciones acentuadas creando muchos microclimas que se diferencian radicalmente no obstante su vecindad

En términos generales los climas que se han encontrado en la Republica Mexicana (Fig 1) son sahariano senegales mexicano estepario senegalés de monzón mexicano de monzón y sudanes

FISIOGRAFIA La Republica Mexicana se ha dividido en nueve zonas cuyos numerosos accidentes crean gran cantidad de valles circundados por cadenas montañosas las más importantes son la Sierra Madre Oriental y la Sierra Madre Occidental con los volcanes de mayor altura Ixtaccihuatl 5 280 m Popocatepetl 5 450 m y Citlaltepetl 5 594 m Entre estas dos cadenas montañosas se encuentra la altiplanicie central en cuya parte sur está localizada la ciudad de Mexico a 2 240 m de altura y a los 19°26 latitud Norte

REGIMENES TERMICOS (Fig 2) Se ha marcado el trópico climatológico que corta tres veces el tropico de Cáncer El área sur posee un regimen termico uniforme con pequeñas variaciones en la temperatura media mensual sin estación invernal propiamente dicha aun en las tierras altas del altiplano

En el área norte [illegible]

FIG 1 — Climas

FIG 2 — Regimen térmico

estaciones del año con variaciones muy benignas para alturas menores de 1 000 m la temperatura llega a tener máxima de 40 °C poco antes de la estación de lluvia En el invierno en las partes altas del norte de la altiplanicie septentrional se presentan algunas nevadas ligeras

De la linea UU a la frontera internacional hay una zona extremosa con verano e invierno acentuados

Regimenes pluviales (Fig 3) Se pueden considerar cuatro zonas

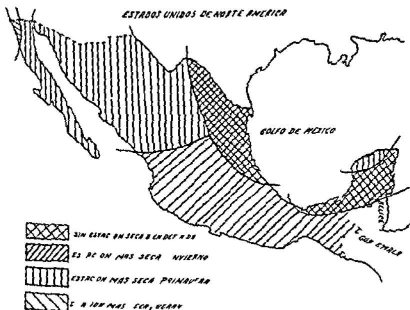


Fig 3 — Regimen pluvial

1º Sin estacion seca bien definida con lluvia en todos los meses independientemente de que en algunos de ellos la frecuencia de ésta sea mayor Cubre la mayor parte de la planicie costera del Golfo de Mexico y serranias vecinas

2º La temporada de sequia queda localizada al invierno Cubre la mayor parte del territorio nacional especialmente el centro y sur

3º Con temporada de sequia en primavera A esta zona pertenece gran parte de la altiplanicie septentrional del norte de la Sierra Madre Occidental la planicie costera del noroeste casi toda la península de Baja California y la porción norte de la de Yucatán

4º La temporada de sequia es en verano Queda limitada esta zona a la región comprendida entre Ensenada Baja California y la frontera internacional

Humedad Es en general condicionada por la proximidad de la costa y los movimientos de las corrientes de aire de la atmósfera superior Las cifras que se han encontrado son 70 % ó más a lo largo de los Estados cercanos

a la costa al sur del tropico de Cáncer, menos de 50 % a lo largo de Sonora en la parte oeste en la meseta central y en el centro de la Baja California Cantidades que varían entre 50 y 70 % en el resto de la nación.

NUBLADOS El sureste particularmente Chiapas tiene alrededor de 150 días de nublados al año La parte noreste los estados del centro y del oeste así como los de la zona sur de la nacion tienen más de 90 dias El mínimo se ha visto al norte de Baja California (30 al ano) en la meseta central se han encontrado 60

ENFERMEDADES ALERGICAS MAS FRECUENTES

Sin poder dar cifras estadísticas es posible señalar de una manera general una incidencia de 1 × 10 considerando los pacientes que han tenido tienen o tendrán manifestaciones alergicas Esta cifra se modificará posiblemente en los proximos años, ya que dia tras día se tiene mas conciencia de estos padecimientos La mayoria de estos enfermos son vistos por el medico general o el dermatólogo siendo de mencionarse que muchos pacientes con la ayuda sintomática que reciben ya no desean someterse a un estudio alergológico

Entre las características de los sindromes alérgicos en México se puede señalar que

1 Generalmente se presentan síntomas asociados bien sea en órganos de choque diferentes (mucosa y piel etc) o aun en distintas porciones del mismo órgano de choque (mucosa nasal y de bronquios) Los casos en que existe sintomatología en un solo órgano de choque non son muy frecuentes

2 En terminos generales puede señalarse que existen polisensibilizaciones siendo los alergenos encontrados de distinto tipo (inhalante ingestante contactante) Los pacientes sensibles a un solo ofensor no son comunes

3 La presencia de infecciones asociadas es muy frecuente tanto en las dermatosis como en las manifestaciones respiratorias En los niños predominan las adenoamigdalianas y en los adultos la de los senos paranasales

Aun cuando los tipos de síndromes alergicos varian segun determinadas zonas de la Republica Mexicana los síntomas respiratorios en términos generales, son los que predominan en particular en el adulto en los niños se están encontrando cada vez con mas frecuencia El factor bacteriano es muy importante en mas de 50 % de los casos y las sensibilizaciones a gérmenes mantienen o desencadenan con mucha frecuencia crisis de asma bronquial o alergias nasales

Hay zonas que hemos denominado asmógenas ya que ahí se encuentran numerosos enfermos y aun cuando existen otros padecimientos en numero importante la relación podría cambiarse a 1 × 5 Están situadas alrededor de la costa, demostrando los estudios realizados que los hongos atmosfericos son de extraordinaria importancia

Los sindromes dermatologicos se observan más en los pequeños sobre todo bajo la forma de prurigo urticaria La dermatitis atópica parece tener la misma incidencia en niños y adultos cuando se presenta en estos últimos su rebeldía al tratamiento es mayor Las reacciones urticáricas son bastante frecuentes en los adultos muchas de ellas son alérgicas siendo desencade

nadas fundamentalmente por alergenos intrínsecos (endoparásitos y bacterias) ingestantes alimentos y drogas

Aun cuando existe toda la enorme gama de síntomas alérgicos los anteriores son los más frecuentes

Entre las manifestaciones de hipersensibilidad quizá peculiares de México se puede mencionar la fotosensibilización en particular en su variedad de actinodermatitis Entre los estudios realizados algunos señalan la coincidencia de que este padecimiento se encuentra en las zonas en que se consume maíz en mayor cantidad

Como reacción alérgica ocupacional mexicana se encuentra la dermatitis de la tortillera Esta trabajadora es la que hace las tortillas (alimento fundamentalmente mexicano) para elaborarlas tiene que colocar un disco de maíz en una fuente de calor con la mano derecha es con la que lo coloca y por eso ese antebrazo queda más cerca de la fuente de calor y es en el precisamente donde se observan las lesiones

ALERGENOS OFENSORES

Varían según los distintos síndromes observados y los diferentes estados de la República Mexicana (la alimentación condiciones higiénicas sanitarias y climatéricas son diferentes en ellos)

INHALANTES Puede decirse que este grupo es el más importante de ellos el polvo el más dañino En la ciudad de México cercana al Lago de Texcoco desecado en febrero y marzo el viento sopla hacia ella originando que en esos meses su atmósfera se encuentre saturada de polvo En Torreón Coah en el centro del altiplano también con extraordinaria frecuencia se presentan tolvaneras lo mismo en otros estados de la República El autor ha encontrado que en el Distrito Federal en esos meses hay mayor número de alergias respiratorias Los tamos de frijol maíz trigo etc son de gran valor ofensor en las regiones agrícolas

HONGOS ATMOSFERICOS Se ha encontrado que son muy importantes en las zonas asr [illegible] paroxismos de
alergia re [illegible]
son las de [illegible]
Se tomó [illegible]
diarios [illegible]

POLENES Aunque son alergenos de importancia no llegan por ningún motivo a alcanzar la que tienen en otros países Clínicamente es indiscutible que hay un buen número de casos de polinosis con manifestaciones tanto bronquiales como nasales pero en la mayoría de ellos existen alergenos asociados

En el Distrito Federal aunque con pequeñas alternancias el autor ha encontrado que las cuentas diarias son las señaladas en el cuadro No II (Informe oficial de la American Academy of Allergy) En términos generales existen

La estación de árboles de noviembre a abril siendo alergénicamente más importante el fraxinus La de pastos de mayo a octubre con máximas cuentas en mayo y septiembre el más importante es el cynodon dactylon

Cuadro I

1955

	ESPORAS						CULTIVOS								
Mes	Td	Al	Ho	He	S	T	Al	As	Ho	He	Pe	Mo	Y	O	T
Enero	17	30			17	47	38	40	7	2	7		3	16	113
Febrero	20	37	5	1	24	67	51	72	9	4	6	4		35	181
Marzo	22	39	4	10	20	73	60	48	1	4	8			34	155
Abril	20	40			18	58	47	41	3	5	9			34	139
Mayo	21	37	13	16		66	36	40	2	5	6	1		30	120
Junio	22	44	14	18		76	40	49	11	13	12	7		28	160
Julio	21	33	16	18		67	39	61	30	12	8			25	1[illegible]5
Agosto	22	33	16	13		62	50	29	17	20	9			35	160
Sepbre	19	34	9	8		51	53	62	16	9	17			51	208
Octubre	22	39	4	6	11	60	63	42	18	10	16			46	195
Novbre	20	27		10	20	57	53	48	28	11	4			48	192
Dicbre	22	40	3	5	22	[illegible]	76	67	45	5	15	8		52	268
TOTAL	248	433	84	105	132	754	606	599	187	100	117	20	3	434	2066

Td Total dias
Al Alternaria
Ho Hormodendrum
He Helminthosporium
S Smut
T Total
As Aspergillus
Pe Penicillium
Mo Monilia
O Otros
R Rust
Y Yeast

Cuadro II

1956	E	F	M	A	M	J	J	A	S	O	N	D	TOTAL
Fresno	173	173	134	92						59	114	215	990
Cedro	319	259	171	1[illegible]4	121					77	162	344	1577
Aliso	110	79	38	40							89	197	553
Zacates			4	33	97	102	92	102	108	110			645
Compuestas					76			88	80	82			326
Amaranthàceas						21	58	63	77				219
Ambrosia								79	191	[illegible]			640

Lc [illegible] de la ambrosia es cuatro para
M [illegible] aun cuando

faltan estudios podría señalarse la siguiente división polínica (Fig 4)

a) Zona central con datos similares a los de la ciudad de Mexico

b) Zona noroeste con bastantes zacates y pastos (amaranthus hibridus y retroflexus franseria tenuifolia ambrosia psylostachia holcus halepen[illegible] y cynodon dactylon

c) Zona norte que tiene también una rica flora alergénica holcus halepensis cynodon dactylon phleum pratense amaranthàceas quenopodiáceas franseria tenuifolia parthenium ligustrum y prosopis

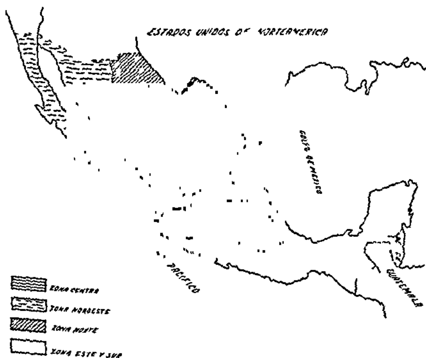


FIG 4 — Zonas polínicas

d) Zona sudeste en la cual aparentemente no existen pólenes alergénicos en cantidad apreciable

OTROS INHALANTES que tienen cierta importancia son las plumas piretro lana y epitelios de animales

ALIMENTO Las diferencias de la comida en los distintos Estados de la Republica Mexicana hacen que estos alergenicamente tengan algunas variaciones En términos generales los más importantes son chocolate huevo leche, trigo maíz mariscos fresas almendra cacahuete nuez mango tomate chícharo frijol

CONTACTANTES Entre ellos además de los ocupacionales el que con más frecuencia se encuentra es la lana

INFECCIONES Son de extraordinaria importancia sobre todo las que están localizadas en garganta nariz aparato digestivo y oídos

INSECTOS Están adquiriendo cada vez mayor valor tanto como contactantes inhalantes e inyectantes Las pulgas chinches mosquitos abejas se han señalado como ofensores con relativa frecuencia

ENDOPARASITO También se han reportado como causantes desencadenantes o mantenedores de síntomas alérgicos en particular ascaris y tenia

METODOS DIAGNOSTICOS

Tienen como base una historia clínica cuidadosa (interrogatorio detallado y exploración física meticulosa), de acuerdo con ella se selecciona el tipo de estudio que debe hacerse

PRUEBAS INTRADERMICAS La mayoría de los alergólogos mexicanos utiliza el metodo intracutáneo siendo la selección de la concentración del extracto segun el grado de hipersensibilidad existente El resultado de las reacciones tardías no se considera muy importante en general sugiere presencia de algun alergeno bacteriano o contaminación secundaria En las pruebas con extractos de parásitos intestinales estudios realizados por el autor parecen indicar que la reacción immediata es específica de especie y la tardía específica de grupo De las pruebas con alimentos los resultados que se esperan obtener son dubitativos pero en algunos casos las respuestas son de valor importante

No se acostumbra hacer un numero sistématico de pruebas sino que la cantidad de ellas se selecciona de acuerdo con el tipo reaccional del paciente

El metodo de transferencia pasiva es utilizado con bastante frecuencia por el autor

Los alergenos son preparados segun los metodos usuales el autor utiliza para desgrasar aquellos que son ricos en lipoides (carnes) el aparato Sothlet

Las pruebas del parche que son un estudio frecuente proporcionan datos definitivos cuando se realizan

Estudios a base de dietas diarios alimenticios etc se llevan a cabo cuando están indicados

Las pruebas con extractos bacterianos o con vacunas solo ocasionalmente se practican

El estudio de leucocitos como metodo de investigacion ha dado resultados interesantes

La busqueda de anticuerpos por el metodo de fijación en superficie ha proporcionado resultados consistentes en algunos padecimientos desencadenados por germenes estudios presentes señalan su bondad en la determinación del tipo sanguíneo así como grandes posibilidades para la identificación de reaginas circulantes

TERAPEUTICA

Se tiene especial cuidado en considerar al enfermo en su conjunto es decir al binomio formado por psiquis y soma y se piensa que se deben corregir y modificar todas las alteraciones fisiopatológicas que desencadera sobre el conjunto el paroxismo alergico

La *terapeutica sintomatica* es similar a la que se utiliza en los demás países La *hiposensibilizacion*, que se realiza siempre que es posible es la *especifica* En terminos generales se usa en los cuadros desencadenados por alergenos inhalantes sobre todo por polvo hongos atmosfericos pólenes lana epitelios de animales plumas obteniendose buenos resultados. Las vacunas bacterianas se utilizan particularmente en los casos de infecciones focales bajo la forma de vacunas autógenas o vacunas autógenas mas

suspensión de los tejidos liofilizados en que existía la infección o bien asociándolas a la histamina

Sólo en contadas ocasiones se realiza la hiposensibilización con alimentos y en casos excepcionales con drogas

La concentración del antígeno utilizado la dosis así como los intervalos están indicados por el tipo de paciente la vía de administración utilizada la mayoría de las veces es subcutánea y la duración del tratamiento está condicionada por la evolución clínica

La *terapeutica inespecífica* como la proteosa de Oriel el azufre precipitado la peptona de Witte es usada con más frecuencia que en otros países siendo los resultados obtenidos bastante alentadores

LA ALERGIA COMO ESPECIALIDAD EN LA MEDICINA MEXICANA DOCENCIA

Debe señalarse que en la actualidad hay un interes creciente en la identificación y estudio de los fenomenos de hipersensibilidad La mayoria de los medicos dedican sólo parte de su tiempo a los enfermos alergicos los que ven unicamente pacientes de este tipo pueden calcularse en 16 estando radicados en las ciudades más importantes Existiendo en la Republica Mexicana aproximadamente 16 000 medicos la proporcion resultante es uno por mil

En la Sociedad Mexicana de Alergistas se agrupan la mayor parte de los alergologos mexicanos realizándose una reunión anual que se efectua en algun Estado de la Republica siempre diferente bajo el patrocinio y en colaboración con la Universidad de ese lugar En el Distrito Federal se celebra una reunión mensual

Por lo que se refiere a la ensenanza ademas de los cursos para postgraduados que organiza la Sociedad Mexicana de Alergistas en la mayoría de las Universidades existe la cátedra (teórica y clínica) de Alergia se imparten tambien en diversos hospitales otros cursos para postgraduados con duracion de un año o seis meses

Por lo que se refiere a la actitud de la poblacion mexicana hacia la alergia se nota en aumento constante el interes hacia las enfermedades alergicas

RESUMEN

La incidencia probable de alérgicos en México es de 1 cada 10 habitantes En general se encuentran sensibilizaciones multiples frecuentemente asociadas con infecciones Los sintomas respiratorios son más frecuentes en los adultos existiendo «zonas asmógenas sobre las costas del país Las manifestaciones dermatológicas más comunes son el prurito y urticaria en los niños la dermatitis atópica en niños y adultos y las reacciones urticarianas en los adultos La actinodermitis tal vez sea una enfermedad peculiar de Mexico y la dermatitis de las «tortilleras» (mujeres que trabajan el maíz) es una enfermedad ocupacional de importancia

METODOS DIAGNOSTICOS

Tienen como base una historia clinica cuidadosa (interrogatorio detallado y exploración fisica meticulosa) de acuerdo con ella se selecciona el tipo de estudio que debe hacerse

PRUEBAS INTRADERMICAS La mayoría de los alergólogos mexicanos utiliza el metodo intracutáneo siendo la selección de la concentración del extracto segun el grado de hipersensibilidad existente El resultado de las reacciones tardías no se considera muy importante, en general sugiere presencia de algun alergeno bacteriano o contaminación secundaria En las pruebas con extractos de parásitos intestinales estudios realizados por el autor parecen indicar que la reacción inmediata es especifica de especie y la tardía específica de grupo De las pruebas con alimentos los resultados que se esperan obtener son dubitativos, pero en algunos casos las respuestas son de valor importante

No se acostumbra hacer un numero sistematico de pruebas sino que la cantidad de ellas se selecciona de acuerdo con el tipo reaccional del paciente

El metodo de transferencia pasiva e utilizado con bastante frecuencia por el autor

Los alergenos son preparados segun los metodos usuales el autor utiliza para desgrasar aquellos que son ricos en lipoides (carnes) el aparato Soxhlet

Las pruebas del parche que son un estudio frecuente proporcionan datos definitivos cuando se realizan

Estudios a base de dietas diarios alimenticios etc se llevan a cabo cuando estan indicados

Las pruebas con extractos bacterianos o con vacunas solo ocasionalmente se practican

El estudio de leucocitos como metodo de investigación ha dado resultados interesantes

La busqueda de anticuerpos por el metodo de fijación en superficie ha proporcionado resultados consistentes en algunos padecimientos desencadenados por germenes estudios presentes señalan su bondad en la determinación del tipo sanguíneo así como grandes posibilidades para la identificación de reaginas circulantes

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Allergenic insects are fleas bedbugs flies and bees

The intradernal tests are generally employed for the diagnosis the type of extracts are chosen and the number of tests decided specially for each patient The extracts are prepared as usual the author employs a Soxhlet apparatus for the defatting

Antibodies are successfully detected by surface fixation tests with serum and enable to diagnosis Brucellose the identification of blood types seems to give good results for the detection of circulating antibodies

Therapeutically we successfully apply non specific treatments We notice a rising interest for allergy in the medical profession and in the public There are about 16 specialized allergologists but most physicians treat allergic patients

The Sociedad Mexicana de Allergistas organises annual meetings in various cities and also post graduate lectures A monthly meeting is held in Mexico City

Most universities give allergic tuition (both theoretical and practical) Post graduate lessons are given in several ho pitals

RÉSUMÉ

Le pourcentage probable de personnes atteintes de troubles allergiques est de 1 sur 10 au Mexique

La cause principale d allergie est la sensibilisation aux pollens souvent associee a des infections Il existe le long des cotes des zones dites Zones Asthmogenes »

Les symptomes respiratoires se rencontrent le plus souvent chez les adultes Les dermatoses sont plus frequentes chez les enfants plus particulierement le prurigo et l urticaire

La proportion d eczema diathesique est sensiblement la meme pour les enfants que pour les adultes les réactions d urticaire sont frequentes chez les adultes

L actinodermatose est peut etre une maladie specifiquement mexicaine ainsi que la dermatose des Tortilleras » (femmes qui pilent le grain pour la « tortilla ») qui semble elle aussi etre une maladie professionnelle spéciale au Mexique

L agent allergene principal est la poussiere de diverses provenances légumineuses mais ble dans les regions agricoles moisissures atmosphériques dans les zones asthmogenes

Il y a une saison du pollen dans la partie centrale de la Republique Mexicaine la saison du pollen des arbres (Fraxinus) de novembre a avril celle du pollen de graminées (Cynodon dactylon) de mai à octobre la saison pour le pollen des plantes joue un role moindre (index 4 pour l Ambrosia) Les plantes et les herbes abondent dans le nord et le nord ouest du pays

Les causes possibles d allergies alimentaires varient d un Etat a l autre chocolat œufs lait blé mais produits de la mer fraises noix mangues legumineuses

Les insectes allergenes sont les puces les punaises les mouches et les abeilles

Pour l etablissement du diagnostic les texts intradermiques sont généralement utilises le type d extrait employe et le nombre des tests est fixé pour chaque sujet

Les extraits sont preparés par les procedes habituels l auteur se sert d un appareil Soxhlet pour procéder a l élimination des matieres grasses

La detection des anticorps est realisée de façon satisfaisante par des tests de fixation de surface faits avec du serum ils permettent de diagnostiquer la Brucellose l identification des types sanguins semble donner de bons resultats pour la detection d anticorps circulants

Du point de vue therapeutique nous employons avec succes les traitements non specifiques

On note dans le corps medical comme dans le public un intéret croissant pour l allergie

Il y a environ 16 allerlogogues specialises mais la plupart des médecins traitent des malades atteints de troubles allergiques

La « Sociedad Mexicana de Allergistos » organise des réunions annuelles dans differentes villes et aussi des cours post scolaires Elle tient une réunion mensuellement a Mexico City

Presque toutes les Universites ont des cours d allergologie tant pratiques que theoriques

Des cours post scolaires sont faits dans quelques hopitaux

ZUSAMMENFASSUNG

Der Prozentsatz von Personen mit allergisch bedingten Storungen betragt in Mexiko ungefahr 1 10

Die hauptsachlichste Ursache der Allergie ist eine Ueberempfindlichkeit gegen Pollen oft vergesellschaftet mit Infektionen Es bestehen entlang der Kuste Zonen die man « asthmogene Zonen » genannt hat

Symptome von Seiten des Respirationsapparates finden sich am haufigsten bei Erwachsenen Dermatosen sind bei Kindern haufiger insbesonders Prurigo und Urtikaria

Das Verhaltnis fur das Diathesie Ekzem ist fur Kinder und Erwachsene gleich urtikarische Reaktionen sind bei Erwachsenen haufig

Die Aktinodermatose durfte eine spezifische Erkrankung fur Mexiko sein wie auch die Trotilleras Dermatose (Frauen die das Korn fur den Tortille zerstampfen) die ebenfalls eine fur Mexiko eigene Berufskrankheit zu sein scheint

Das hauptsachliche Allergen ist der Staub verschiedener Herkunft Gemuse Mais Getreide in den bauerlichen Regionen Luft schimmelpilze in den asthmogenen Zonen

Es gibt Pollen Jahreszeiten in der Zentralgegend der mexikanischen Republik Die Saison fur Baumbluten (Fraxinus) von November bis April die Jahreszeit fur Graspollen (Cynodon Dactylon) von Mai bis Oktober ie Saison fur Pflanzenpollen spielt nur eine mindere Rolle (Index fur Ambrosia 4) Die Pflanzen und Graser sind im Norden und Nord Westen des Landes reichlich vorhanden

Die moglichen Ursachen einer Lebensmittelallergie variieren von einem

Staat zum anderen Schokolade Eier Milch Getreide Mais Meeres produkte Erdbeern Nusse Mangofruchte Gemuse

Insektenallergene sind Flohe Wanzen Fliegen und Bienen

Fur die Diagnostik werden im allgemeinen Intradermalteste verwendet der verwendete Extrakttyp und die Anzahl der Teste ist fur jeden Stoff fixiert

Die Extrakte werd n nach den gelaufigen Prozeduren hergestellt der Autor verwendet einen Soxhlet Apparat um Fettsubstanzen zu eliminieren

Die Aufdeckung von Antikorpern wird in zufriedenstellender Manier mit Oberflachenfixationstesten durchgefuhrt sie gestatten die Brucellose zu diagno tizienen die Identifizierung von Bluttypen scheint gute Resul tate fur das Aufdecken zirkulierender Antikorper zu geben

Vom therapeutischen Standpunkt aus verwenden wir mit gutem Erfolg unspezifische Behandlungsmethoden

Man stellt sowhol in Arztekreisen als auch in der Allgemeinheit zuneh mendes Interresse fur die Allergie fest

Es gibt ungefahr 16 Allergologisten aber die meisten Ärzte behandeln Kranke mit allergischen Storungen

Die Sociedad Mexicana de Allergistos (mexikanische Vereinigung der Allergologisten) veranstaltet jahrliche Zusammenkunfte in den ver schiedenen Stadten und auch Fortbildungskurse In Mexiko City veranstal tet sie mona liche Zusammenkunfte

Fast alle Universitaten fuhren sowohl praktische als auch theoretische Allergologiekurse durch

Fortbildungskurse werden von manchen Krankenhausern veranstaltet

PORTUGAL

par

MARIO DAMAS MORA

(Service des maladies allergiques de la Junta de Provincia da Estremadura Lisboa)

Le Portugal jardin de l Europe chante par les poetes morceau de terre avec une surface de 9 000 km borde au nord et a l est par l Espagne et au sud et a l ouest par l Océan Atlantique jouit d un climat privilegie grace a sa position geographique et à la proximité du Gulf Stream

Avec une population de 9 000 000 environ d habitants il y a dans le pays une diver ité de sous climats interessant differentes regions Dans ces sous climats les micro climats ont les varietes les plus inegales

Dans un travail recemment discuté au II^e Congres International d Asthmologie qui eut lieu a Lisbonne en octobre 1957 on constata l influence du climat comme un facteur provocateur de crises d allergie Ce fait est tres important etant donne qu il depend du développement de certaines especes botaniques qui causent par leur production pollinique des sensibilisations allergiques spécifiques

Selon les travaux de ma compatriote Quiteria G Pinto da Silva la pollinisation de l air dans certaines regions du pays augmente brusquement en avril et atteint son maximum en mai (124 1 a 598 7 grains de pollen par cm)

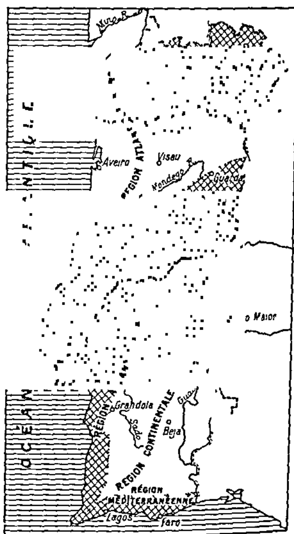
L analyse des moyennes mensuelles en 1950 met en evidence l existence d une saison pollinique printaniere et d une autre legere et d une courte duree au debut de l automne (octobre)

Les especes suivantes sont communes au Portugal *Cupressus sempervirens* — *Pinus parietaria officianlis* — *Graminées* (le pollen de graminees a ete considere comme un des principaux agents de pollino e étant donne sa toxicite allergique — Woodhouse 1945) — *Olea europera* — *Quenopodeaceas* et *Amarantaceas* — *Xanthium* et *Artemisia* — *Plantago*

Des tests effectues chez un grand nombre d individus ont revélé une grande positivité aux pollens de Dactylis Hordeum Festuca Secale cereale Polypogon Zea Mays

Etant donne qu il n y a pas chez nous de service specialise pour l étude et le traitement des maladies allergiques il est impossible de nous faire une idee complete sur l importance de ce fléau

Dans le petit service officiel qui se trouve sous ma direction qui est consacre aux maladies allergiques et qui est maintenu par la Junta de la Province d'Estremadura on a observe et traité pendant les six dernieres annees environ 8 000 allergiques appartenant a des classes economiquement faibles



Régions climatiques du Portugal

Si l'on ajoute a ce chiffre les 4 000 malades environ de la clinique non officielle, et en tenant compte des renseignements fournis par d'autres allergistes du pays on constate que le pourcentage d'allergiques au Portugal ne doit pas etre tres eloigné des chiffres publiés par l'International Association of Allergists au I[er] Congres International de Zurich

... chez nous environ 50 % sont d'on... ...orme de rhinites allergenes ... d'injection) 35 % relevent

des facteurs allergico inflammatoires ou allergico infectieux (bronchites d'origine ou « épine irritative » tuberculeuse) et les 15 % restants relèvent d'affections dans lesquelles on ne peut envisager l'existence d'un facteur allergique

A la suite des contacts fréquents que j'ai avec le service du Professeur Pasteur Vallery Radot à l'Hôpital Broussais à Paris j'ai pu adopter pour mon service au Portugal en ce qui concerne les études cliniques expérimentales et thérapeutiques sur l'allergie la même orientation quoique modifiée en quelques petits détails que celle de l'École Française On a organisé un groupe de spécialistes qui suivant les mêmes principe a effectué un travail scientifique important

En outre la Société Portugaise d'Allergie où sont groupés les allergistes portugais peut maintenant s'enorgueillir de la présence de spécialistes tels que Joao Correia Guimaraes Dias de Andrade Ramos Castano Quaresma de Matos Baiao da Silva Piedade Guerreiro Pereira da Conceiçao Vasques Lopes Jeremias da Silva Lopes de Carvalho outre les Professeurs Adelino Padesca Cerqueira Gomes et beaucoup d'autres qui ont apporté leur contribution

Certains travaux sur l'A C T H le métabolisme de l'histamine certaines pollinoses la crénothérapie des allergies la valeur de l'éosinophilie l'action de la prednisolone (commercialisée au Portugal sous la forme injectable et sous le nom de Lepicortinolo) les antibiotiques les extraits poly allergeniques tel que l'Asmalergil du Professeur Gianfranco Capuani et beaucoup d'autres ont été méthodiquement publiés comme une contribution modeste portugaise à l'étude mondiale des maladies allergiques

Étant donné que les possibilités de recherches sont assez limitées le travail se faisant dans un milieu sceptique sinon hostile où la grande majorité des personnes à commencer par quelques gouvernants responsables considèrent les manifestations d'allergie comme un accident vulgaire et simple et sans la reconnaissance officielle de cette spécialité par l' Ordem dos Medicos » (Association des Médecins) on doit reconnaître aux collègues précurseurs de l'étude des maladies allergiques au Portugal le mérite et leur accorder notre admiration et sympathie pour l'abnégation et l'esprit de sacrifice révélés par leur persévérance

Il n'y a que peu de dispositions législatives au Portugal pour la protection de l'ouvrier qui s'expose à l'action des allergènes sensibilisants par la nécessité de son travail Ainsi nous n'avons que la loi nº 1942 du 27 juillet 1936 concernant les accidents de travail et maladies professionnelles laquelle permet d'envisager favorablement la protection des sujets sensibilisés pendant leur travail quotidien pourvu qu'ils soient inclus dans l'organisation corporative

Les dispositions de cette loi sont les suivante

Chapitre I

Art 1er — *On accordera l'assistance clinique quelle que soit la manière dont elle est administrée y compris les médicaments ainsi que les indemnisations établies par cette loi à tous les ouvriers employés par d'autres personnes lesquels peuvent être victimes d'accidents de travail leur causant une lésion ou maladie dans les cas suivants*

1° *Au local etc pendant la période de travail*

Er referiert dann das einzige vorhandene Gesetz zum Schutz der Arbeite gegen Berufskrankheiten und Schaden das vom 27 Juli 1936 stammt und er erwahnt auch das vom portugiesischen « Minister der Gilden » gegebene Versprechen die offizielle Liste der Berufkrankheiten bezuglich allergischer Krankheiten neu zu bearbeiten

RESUMEN

Dado que no existen estadisticas oficiales debido a la falta de servicios especializados de investigación y tratamiento de enfermedades alergicas el autor se limita a presentar la informacion obtenida en su servicio de la Junta de la Provincia de Extremadura y la de algunos colegas especializados en el tratamiento de las afecciones alérgicas

De acuerdo con las cifras presentadas por la I A A en el Ier Congreso Internacional de Alergología en Zurich se refiere a las conclusiones de la 2a Conferencia Internacional de Asmología en Lisboa en octubre de 19 , sobre la «necesidad de estudiar una legislación destinada a la proteccion de la salud de los obreros y a la defensa de los pacientes de asma profesional» Al mismo tiempo llama la atención sobre la influencia del clima sobre e desarrollo de las enfermedades alergicas que son producidas por los polen de ciertas especies botánicas

El autor se refiere a la unica ley de proteccion de los accidentes de trabajo y las enfermedades profesionales que data del 27 de julio de 1936 y a la promesa del Ministro portugues de las Corporaciones de actualizar la lista de las enfermedades profesionales teniendo en cuenta las sensibilizaciones alergicas

des facteurs allergico inflammatoires ou allergico infectieux (bronchites d'origine ou « épine irritative » tuberculeuse) et les 15 restants relèvent d'affections dans lesquelles on ne peut envisager l'existence d'un facteur allergique

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1º *Au local etc pendant la période de travail*

2° *Pendant le travail hors du local et la periode de travail normal si l accident a lieu pendant l execution d ordres ou services sous l autorité patronale*
3° *Pendant l execution de services rendus spontanement par les ouvriers à l entite patronale si celle ci peut en obtenir des benefi es économiques*
§ unique — *Si la lésion ou la maladie n est pas reconnue immédiatement apres l a cident la victim devra fo irnir les preuves nécessaires que celle ci est u i conséquen e de cet accid nt*

Art 6 — *Les dispositions d cette loi sont applicables aux maladies professionnelles suivantes*
a) *Intoxication par plomb, etc*
b) *Intoxication par mercure etc*
c) *Intoxication par l action de colorants et dissol ants nuisibles*
d) *Intoxication par l action de poussieres gaz et vapeurs industriels*
e) *Intoxication par l action des rayons X ou de substances radioactives*
f) *Injection charbonneuse*
g) *Dermatoses professionnelles*

La IIe Conference Internationale d Asthmologie qui a eu lieu a Lisbonne a attire l attention des organismes officiels du mond entier sur « la nécessité d étudier une legislation destinee a la protection de la sante des ouvriers et a la défense des droits de ceux qui sont atteints par l asthme professionnel »
En portant a la connaissance du Ministre des Corporations les conclusions de la Conference la Société Portugaise d Allergie a attire l attention du Ministre sur l importance du problem de l allergie au Portugal Selon les statistiques publiées environ 85 000 individus c est à dire environ 1 % de la population to ale du pays sont atteints d asthme
Les allergistes portugais espèrent que par l entremise de leur Société on demandera leur collaboration pour le reglement officiel de ce probleme et qu on pourra ainsi organiser un ou plusieurs Centres de recherches et de traitement d asthme et des maladies allergiques ce dont nous sommes si désireux car cela est necessaire pour l etude rationnelle de la lutte contre ces maladies

RÉSUMÉ

L auteur n ayant pas d élements statistiques officiels par manque de services spécialises de recherches et traitements des maladies allergiques se borne a presenter les informations obtenues dans son service de la « Junta de Provincia da Estremadura » et des collegues spécialises dans le traitement des affections allergiques D accord avec les chiffres presentes par l I A A au Ier Congrès International d Allergologie à Zurich il rappelle les conclusions de la IIe Conférence Internationale d Asthmologie à Lisbonne en octobre 1957 sur « la necessité d étude d une législation destinée à la protection de la santé des ouvriers et à la défense des droits de ceux qui sont atteints par l asthme professionnel » En meme temps il attire l attention sur l influence du climat dans le développement des affections allergiques

conséquence de l'existence de certaines espèces [illegible] qui déterminent par leur production pollinique des sensibilisations [illegible] tiques.

Il se réfère à la seule loi de protection [illegible] et les maladies professionnelles datant du [illegible] donnée par le Ministre portugais des Corporations [illegible] des maladies professionnelles au point [illegible] giques.

SUMMARY

As there are no official statistical data available [illegible] medical services for allergic therapy and allergy [illegible] the author will only give information gathered in his district [illegible] Junta de Província da Estramadura and among [illegible] lizing in the treatment of allergic diseases.

The author agrees with the figures set forth [illegible] time of the first Allergological Congress held in Zurich and [illegible] conclusions of the second International Conference [illegible] Asthma held in Lisbon in October 1957) with regards to the necessity to [illegible] legal measures [illegible] the purpose of protecting worker's health and to look [illegible] the rights of workmen suffering from occupational asthma.

Attention is drawn to the influence exerted by the climate in the [illegible] of allergic diseases due to pollens of certain botanical species which are responsible for specific allergic sensitizations.

The author then refers to the only existing law regulating the protection of workmen against injuries and occupational illnesses; this law dates from the 27th of July 1936 and he also mentions the promise made by the Portuguese Minister of corporations to add the allergic diseases to the official list of the occupational diseases.

ZUSAMMENFASSUNG

Da in Portugal keine offiziellen statistischen Unterlagen zur Verfügung stehen und ausserdem keine auf Allergieforschung und Allergiebehandlung spezialisierten Anstalten vorhanden sind, wird der Autor nur Informationen geben können, die er in seinem Bezirk (Junta de Província da Estramadura) und unter seinen auf Asthmabehandlung spezialisierten Kollegen gesammelt hat.

Der Autor stimmt den Entschlüssen zu, die von der I. A. A. am ersten Allergiekongress in Zürich gefasst worden waren und er erinnert an die Beschlüsse der zweiten internationalen Asthmakonferenz in Lissabon (Oktober 1957), die den Zweck verfolgten, gesetzliche Massnahmen zum Schutze der Gesundheit des arbeitenden Menschen zu finden und für die Verteidigung der Rechte der an Berufsasthma erkrankten Arbeiter zu sorgen.

Der Einfluss des Klimas auf die Verbreitung allergischer Erkrankungen wird beachtet von Erkrankungen, bei denen Pollen gewisser botanischer Species für die spezifische allergische Sensibilisierung verantwortlich sind.

Er referiert dann das einzige vorhandene Gesetz zum Schutz der Arbeiter gegen Berufskrankheiten und Schäden das vom 27 Juli 1936 stammt und er erwähnt auch das vom portugiesischen « Minister der Gilden » gegebene Versprechen die offizielle Liste der Berufskrankheiten bezüglich allergischer Krankheiten neu zu bearbeiten

RESUMEN

Dado que no existen estadísticas oficiales debido a la falta de servicios especializados de investigación y tratamiento de enfermedades alérgicas el autor se limita a presentar la información obtenida en su servicio de la Junta de la Provincia de Extremadura y la de algunos colegas especializados en el tratamiento de las afecciones alérgicas

De acuerdo con las cifras presentadas por la I A A en el Ier Congreso Internacional de Alergología en Zurich se refiere a las conclusiones de la 2a Conferencia Internacional de Asmología en Lisboa en octubre de 1957 sobre la necesidad de estudiar una legislación destinada a la protección de la salud de los obreros y a la defensa de los pacientes de asma profesional. Al mismo tiempo llama la atención sobre la influencia del clima sobre el desarrollo de las enfermedades alérgicas que son producidas por los polenes de ciertas especies botánicas

El autor se refiere a la única ley de protección de los accidentes de trabajo y las enfermedades profesionales que data del 27 de julio de 1936 y a la promesa del Ministro portugués de las Corporaciones de actualizar la lista de las enfermedades profesionales teniendo en cuenta las sensibilizaciones alérgicas

BELGIQUE

par

Jacques DUCHAINE

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La Belgique, pays de modeste étendue (30.506 km²) est par contre un des plus peuplés du monde : 9 millions d'habitants recensés à la fin de l'année 1956.

Le relief est peu accusé, sauf dans la partie orientale où s'élève le plateau des Ardennes, région de collines, de bois, à population clairsemée par suite de la pauvreté du sol. En fait, la majeure partie des habitants est concentrée dans les régions de la basse et moyenne Belgique où se trouvent les grandes villes, les centres industriels et où la fertilité du sol a permis la culture intensive des céréales et des plantes industrielles (betterave sucrière, colza) et le développement important de l'élevage.

Le climat est tempéré, sans grandes variations de la température, humide, sujet aux brouillards par suite de la proximité des grands fleuves : Meuse, Escaut et Rhin qui se jettent dans la Mer du Nord. Dans l'Est du pays, le climat est plus rude et plus sec et la neige y est souvent abondante durant une partie de l'hiver.

Ces conditions climatiques et sociales favorisent incontestablement l'éclosion des maladies allergiques et elles contribuent à aggraver leur évolution surtout en ce qui concerne l'allergie respiratoire. Le nombre d'asthmatiques semble être assez élevé et, dans la majorité des cas, il existe certainement un facteur allergique à la base de leur affection.

L'allergène dominant est la poussière de maison et la source principale s'en trouve dans la literie. Depuis une dizaine d'années, l'usage de literies en latex de caoutchouc ou en fibres synthétiques tend à se répandre mais il est difficile d'apprécier l'influence que celles-ci pourraient avoir sur la courbe de la morbidité asthmatique. Néanmoins, les matelas en poils de lapin, fort prisés avant 1940, ont été presque entièrement abandonnés et il est tout à fait exceptionnel de rencontrer une sensibilisation à cet allergène chez l'enfant, chose qui était encore très fréquente il y a quelques années.

Divers facteurs locaux importants contribuent à aggraver l'asthme en Belgique. Les automnes et les hivers brumeux favorisent les poussées infectieuses et, dans les centres industriels, les brouillards chargés de vapeurs toxiques (smog) exercent une influence extrêmement néfaste sur

les malades dont l équilibre respiratoire est instable Heureusement les essais effectués depuis plus de deux ans semblent montrer que les conséquences en peuvent être efficacement combattues par les corticostéroïdes

I PRINCIPALES MALADIES ALLERGIQUES

Comme la terre est cultivée dans ses moindres recoins (sauf dans les Ardennes) les forêts sont rares et les espèces anémophiles autres que les graminées sont peu répandues Mais ces dernières sont très abondantes dans tout le pays et la saison de la pollinose est courte (4 à 5 semaines) mais sévère Les cas de sensibilisation au pollen des arbres sont très rares et les quelques cas de pollinose aux composées qui ont été dépistés concernaient des jardiniers ou des individus qui avaient séjourné durant plusieurs années aux Etats Unis En fait la seule composée anémophile dont le pollen pourrait se montrer nocif est *artemisia* et il semble bien qu elle soit si peu répandue que la densité de son pollen dans l atmosphère n atteint jamais le seuil critique

L allergie respiratoire due aux spores de moisissures atmosphériques est beaucoup moins fréquente que ne semblerait l indiquer le résultat des tests cutanés En fait grâce aux épreuves de provocation nous avons pu dépister quelques sensibilisations a *alternaria* et a *cladosporium* mais aucune jusqu à ce jour aux autres moisissures

L eczéma atopique est peu répandu tout au moins chez l adulte et la sensibilisation aux poussières domestiques nous semble y jouer un rôle plus important que l allergie alimentaire

Par contre l urticaire et l œdème angioneurotique sont le plus souvent d origine alimentaire et surtout médicamenteuse L usage généralisé des antibiotiques des barbituriques des laxatifs semble avoir multiplié la fréquence de ces allergies

Il en est de même de l allergie professionnelle dont l augmentation est sans doute due en partie à l amélioration des techniques du diagnostic mais aussi à la création de nouvelles industries où se manipulent un grand nombre d allergènes puissants (industries chimique pharmaceutique alimentaire etc)

II STATISTIQUES

a) Mortalité

Ce n est que depuis l année 1954 qu il existe des statistiques valables sur les causes de décès en Belgique Un nouveau modèle de bulletin de déclaration confidentiel fut introduit à cette date et la nomenclature adoptée est conforme au règlement de l Organisation mondiale de la Santé

Le tableau I nous donne le détail de la mortalité pour l asthme allergique établi pour l année 1954 suivant les déclarations des médecins traitant Il nous semble utile de le compléter par le tableau II qui résume la mortalité par bronchite chronique pendant la même période Il n est que trop certain que de nombreux cas étiquetés bronchites chroniques rentreraient dans la *catégorie de l asthme allergique si le diagnostic étiologique* en avait pu être fait avec plus de compétence (Que faut il penser des 15 enfants de 0 à 5 ans morts de bronchite chronique ?)

Tableau I

Mortalité par asthme allergique en 1954 (1)

Groupes d'âge	Répartition de la population	Nombre de décès par asthme allergique			Nombre de décès par 100 000 habitants
		H	F	Total	
5 ans	606 120	5	2	7	1
10 —	681 879	—			—
15 —	533 931	2		2	0 38
20 —	5 6 616	2		2	0 35
25 —	631 444	2	2	4	0 63
30 —	653 780	4	2	6	0 92
35 —	695 057	—	8	8	1 15
40 —	450 926	—	1	8	1
45 —	632 033	9	10	19	3 01
50 —	642 406	18	15	33	5 15
55 —	630 062	32	15	47	7 46
60 —	550 106	46	28	74	13 45
65 —	449 565	65	24	89	20 22
70 —	373 37[illegible]	66	39	105	31 62
75 —	297 024	51	32	83	25 17
80 —	200 548	40	41	81	40 5
85 —	102 281	25	23	48	48
+ 85 —	43 749	13	14	27	67 5
Total	8 840 704	387	256	643	7 04

Tableau II

Mortalité par bronchite chronique en 1954 (1)

Groupes d'âge	Nombre de décès par bronchite chronique			Nombre de décès par 100 000 habitants
	H	F	Total	
5 ans	8	7	15	2 17
10 —	—	—	—	—
15 —	—	—	—	—
20 —	1	—	1	0 17
25 —	—	—	—	—
30 —	—	2	2	0 3
35 —	3	2	5	0 72
40 —	4	—	4	0 88
45 —	9	1	10	1 42
50 —	30	4	34	5 31
55 —	53	7	60	9 52
60 —	105	17	122	22 18
65 —	140	27	167	37 95
70 —	187	29	216	58 38
75 —	161	60	221	76 2
80 —	127	95	222	111
85 —	89	66	155	155
+ 85 —	42	43	85	212 5
Total	959	360	1 319	14 92

Néanmoins si nous comparons les chiffres du tableau I aux statistiques pour l'Angleterre et le Pays de Galles (année 1944) publiées par D A Williams (3) nous pourrons constater qu'ils correspondent à peu de chose près (73 décès par million d'habitants en Belgique pour 70 en Angleterre)

Cette comparaison est d'ailleurs tout à fait valable car la Belgique et l'Angleterre présentent toutes deux des courbes démographiques parallèles et la répartition de la population suivant l'âge et le sexe y est pratiquement la même

Notons enfin que la mortalité par asthme allergique et bronchite chronique (2 513 décès) dépasse largement le total de 1 696 tuberculeux pulmonaires morts durant la même période

b) Influence de l'industrialisation sur la mortalité des affections non tuberculeuses des voies respiratoires

La Belgique est divisée administrativement en neuf provinces dont deux (Liège et le Hainaut) sont fortement industrialisées et comprennent les grands centres de l'industrie lourde (fer et charbon) Les provinces d'Anvers du Brabant des deux Flandres du Limbourg bien que fort peuplées ont conservé une importante activité agricole Enfin les provinces du Luxembourg et de Namur sont essentiellement agricoles et leur population est plus réduite que celle des autres parties du pays

Il n'existe pas de statistiques concernant la mortalité par asthme pour les diverses provinces mais on peut s'en faire une idée assez nette grâce au tableau III qui résume le nombre de décès par affections des voies respiratoires à l'exclusion de la tuberculose et du cancer Il est indéniable que l'industrialisation constitue un facteur d'aggravation des maladies respiratoires (et par conséquent de l'asthme qui est ici compris dans la même rubrique)

Tableau III

Décès par affections non tuberculeuses des voies respiratoires dans les neuf provinces de Belgique ([1])

Provinces	Population	Nombre de décès par affections des voies respir (T exclue)	Nombre de décès par 100 000 habitants
Hainaut	1 253 558	2 012	16 7
Liège	989 668	1 286	14 3
Anvers	1 352 330	1 274	9
Brabant	1 874 168	1 471	8 1
Flandre orient	1 246 060	1 241	10 3
— occident	1 246 060	834	6 9
Limbourg	517 561	341	6 8
Luxembourg	216 431	238	1 1
Namur	363 462	462	1 2

c) Morbidité

Au moment de rédiger ce rapport, malgré nos recherches, il nous a été . . . . . . mettant des . . . . *) Les . . . or talité celles des grands hôpitaux ou cliniques ne donnent que la proportion des asthmatiques par rapport au nombre total des malades ayant eu recours à leurs soins. Mais même lorsque ces dernières statistiques ont été établies avec tout le soin nécessaire, elles refléteront immanquablement la spécialisation plus ou moins poussée en allergie du service des voies respiratoires. Il est certain qu'un chef de service qui s'intéresse particulièrement aux choses de l'allergie draînera la clientèle correspondante et que ses statistiques seront artificiellement gonflées.

Néanmoins, comme les résultats de plusieurs examens de collectivités ont été publiés et que ceux-ci ne comprennent que la rubrique « affections des voies respiratoires à l'exclusion de la tuberculose », il serait intéressant de pouvoir se rendre compte de la proportion approximative d'allergiques parmi ces malades respiratoires.

Nous possédons deux séries de statistiques à ce sujet et, dans les deux cas, elles se rapportent à un service de pneumologie où les diagnostics d'allergie ont été établis avec tout le soin désirable : 1° Un service de pédiatrie dans un hôpital central de Bruxelles : 77 p. 100 de cas d'allergie sur 280 cas pulmonaires (enfants de 0 à 15 ans). 2° Un service de pneumologie dans un groupe médical : 76 p. 100 d'allergiques sur 1 837 malades (enfants et adultes).

Nous pouvons donc poser en principe que chez 76 p. 100 des malades souffrant d'affections chroniques des poumons, il existe un facteur allergique tout au moins comme base de leur maladie.

Ces chiffres ne sont valables que pour les allergies respiratoires (qui constituent la majeure partie des allergies atopiques) car, à notre connaissance tout au moins, il n'existe aucune donnée qui puisse nous mettre sur la voie de l'importance relative des autres affections allergiques : eczéma de contact, urticaire, migraine, etc., dont le pourcentage de morbidité doit être assez élevé mais dont la mortalité est pratiquement nulle.

d) Coût de la maladie

Lors de la tutelle sanitaire des agents de l'État en 1954, sur 123 481 malades examinés, 15 433 ont été reconnus atteints de troubles des voies respiratoires (à l'exclusion de la tuberculose et du cancer) (2). Si le chiffre de 76 p. 100 d'allergiques cité ci-dessus est exact, nous en concluerons que 11 7 9 étaient des allergiques respiratoires (soit 9 p. 100 des malades examinés).

De même, sachant que 240 301 jours de congé ont été attribués aux malades pulmonaires, nous en déduirons que nos 11 729 allergiques ont bénéficié de 181 168 jours d'absence, soit 16 journées par an et par malade allergique.

(*) Il se pourrait qu'une documentation concernant les examens d'aptitude à l'armée ou le résultat d'enquêtes parmi les collectivités soit publiée au cours des mois prochains. Dans l'affirmative, nous ne manquerons pas d'en faire état lors de la discussion du présent rapport.

Néanmoins l'effort est encore trop sporadique et surtout trop récent pour qu'on puisse affirmer que l'enseignement de l'allergologie y soit établi sur des bases définitives

Précisons en outre qu'il existe à Liège un centre de recherches expérimentales où sous l'impulsion du Dr Jean Lecomte on étudie le métabolisme de l'histamine et des histamino libérateurs sur l'animal et en clinique humaine

Dans la même ville une étude systématique de l'eczéma professionnel est poursuivie par Mme le Docteur van Cauwenberge dans le service de Dermatologie du Professeur Lapière

IV NOMBRE DE MÉDECINS ALLERGISTES

Pour une population de 9 millions d'habitants la Belgique compte environ 10 000 docteurs en médecine Parmi ceux ci 8 peuvent être considérés comme allergistes à plein temps leur pratique s'adressant exclusivement aux malades allergiques Une vingtaine d'autres tout en étant spécialisés en pneumologie en médecine interne ou en O R L font bénéficier leurs malades des techniques et traitements allergologiques qu'ils ont approfondis Il est à remarquer que 4 parmi ces 8 allergistes travaillent dans les services hospitaliers universitaires de médecine interne à Louvain ou de pédiatrie à Bruxelles et que les 4 autres appartiennent à des groupes médicaux polycliniques du secteur privé Ceci confirme le fait que la pratique exclusive de l'allergie ne peut être fructueuse que si elle s'opère en milieu hospitalier ou tout au moins que si elle conserve des rapports étroits avec la médecine interne les autres spécialités et notamment avec l'O R L et la dermatologie

Il n'est pas téméraire d'affirmer que au point de vue formation ces 8 allergistes sont des autodidactes et que s'ils ont puisé la base de leurs connaissances dans les traités français allemands et anglo saxons ils ont surtout été façonnés par la rude école de la pratique quotidienne Au début de leur carrière tous ont suivi les cours de perfectionnement organisés chaque année à l'Hôpital Broussais par le Professeur Pasteur Vallery Radot dont l'influence a souvent été déterminante dans le choix de leur spécialisation ultérieure

V SOCIÉTÉS SCIENTIFIQUES

Bien que des communications ayant trait à l'allergie soient assez souvent présentées devant l'une ou l'autre assemblée scientifique seule la Société Belge d'Allergologie s'occupe exclusivement de l'allergie clinique ou expérimentale Fondée en juillet 1946 elle comprend 38 membres payant régulièrement leur cotisation et un nombre plus élevé de membres moins prodigues de leur patrimoine

Au début la Société Belge d'All renseigner ses auditeurs sur les tr années de guerre lorsque les relat entre la Belgique et les centres de

peu d intérêt que le corps médical avait toujours manifesté même avant la guerre envers une spécialité qui pouvait sembler n avoir acquis droit de cité qu aux seuls États Unis elle organisa une série de conférences destinées à éclairer les médecins sur les caractéristiques fondamentales de la pratique allergologique Cette action dont l utilité est incontestable fut entravée par diverses difficultés matérielles (p ex impossibilité de se procurer des extraits allergéniques efficaces sur le marché belge) mais surtout par l absence d une tradition féconde qui aurait pu soumettre nos erreurs d interprétation à l arbitrage de critères valables

A l heure actuelle la Société Belge d Allergologie organise régulièrement des réunions amicales ou sans formalisme excessif sont mis en discussion certains aspects fondamentaux de l activité professionnelle citons valeur comparative des différents extraits allergiques commerciaux rôle des antigènes alimentaires traitement par les corticostéroïdes statistiques recueillies par les membres présentation de cas mises au point etc Les travaux originaux sont plus rares car la majorité de ceux ci sont présentés lors des congrès internationaux qui se succèdent à un rythme accéléré

Récemment la Société Belge d Allergologie a eu son attention attirée sur un fait qui mérite d être examiné attentivement Sous l influence de diverses firmes commerciales mettant en vente des boîtes d extraits destinés aux tests cutanés de nombreux médecins pratiquent ces épreuves sans ordre et sans méthode et par défaut d expérience ou d esprit critique ils imposent souvent à leurs malades des traitements dits de désensibilisation spécifique qui ne désensibilisent rien et ne sont certainement pas spécifiques *Nous voyons aussi certains médecins adresser leur patient à des laboratoires d analyses biologiques en les priant de le tester pour voir à quoi il est allergique !*

Ces pratiques sont le témoignage certain de l ignorance encore répandue dans une grande partie du corps médical des techniques courantes de l allergologie et portent en elles le danger d une dégradation continuelle de la confiance que notre spécialité devrait inspirer Les allergistes belges estiment qu il s agit là d une de ces maladies infantiles qui frappent régulièrement les jeunes spécialités médicales et que seule la diffusion d un enseignement adéquat peut utilement combattre mais ils n en regrettent pas moins que jusqu à ce jour les facultés de médecine semblent vouloir demeurer étrangères à celle ci

VI SÉCURITÉ SOCIALE

La Sécurité Sociale ou Fonds National d Assurances Maladie et Invalidité est destinée à aider financièrement ses cotisants c est à dire la très grande majorité des habitants du pays frappés par la maladie ou le chômage

Les diverses prestations médicales ont été codifiées en 1945 lors de la création de la S S Elles n ont subi que peu de changements depuis lors et aucune des techniques utilisées couramment par l allergiste (tests cutanés épidermo réactions Prausnitz Kustner épreuves fonctionnelles pulmonaires etc) n y sont mentionnées et elles ne donnent donc pas droit légal à remboursement Il en était de même de certains médicaments couteux

comme les corticosteroides mais depuis peu la prednisone sous prescription magistrale est admise au remboursement integral Malgre cela il est incontestable que les malades allergiques doivent supporter personnellement la plus grande part des frais medicaux eleves qu en traine le traitement d une affection chronique plus que toute autre sujette à des rechutes

VII GROUPEMENT PROFESSIONNEL

La Securite Sociale reconnait le fait de la specialisation en medecine en accordant un tarif preferentiel aux medecins legalement reconnus comme specialistes Ceux ci ont forme divers groupements professionnels destines à défendre leurs interets et a etablir les criteres d admission des candidats.

Les allergistes sont actuellement en nombre trop restreint pour songer à se grouper sur le plan professionnel La plupart sont d ailleurs reconnus comme specialistes mais dans les disciplines (pneumologie medecine interne pediatrie O R L) qu ils pratiquaient avant de se consacrer exclusivement a l allergie

Cependant il n est pas interdit de penser que lorsque la pratique de notre specialite aura touche un plus grand nombre de medecins surtout parmi les jeunes sortant de l Universite la création d une Union professionnelle des Allergistes ne s impose comme une necessite absolue

VIII ARMEMENT MÉDICO SOCIAL POUR MALADES ALLERGIQUES

La fondation d établissements pour enfants asthmatiques s avere etre indispensable si nous desirons lutter efficacement contre les maladies allergiques au moment ou elles sont le plus accessibles à nos moyens therapeutiques c est a dire durant l enfance

Cette nécessite a retenu l attention du Ministere de la Sante publique et il se pourrait que bientot quelques sanatoria depeuples par la reduction du nombre de tuberculeux hospitalisés soient transformés en homes pour enfants asthmatiques ou eczemateux

Mais la encore l obstacle principal reside dans le nombre insuffisant des medecins competents en allergie et qui pourraient consacrer leurs efforts à cette nouvelle tâche Il en est de meme du personnel infirmier et il est urgent que les ecoles d infirmieres et d assistantes sociales *dispensent* a leurs eleves quelques notions d allergologie

IX PERSPECTIVES D AVENIR DE L ALLERGOLOGIE EN BELGIQUE

Malgre toutes ces lacunes les perspectives pour l avenir ne sont pas mauvaises Mais avant que les allergistes belges puissent entreprendre des travaux scientifiques de longue haleine ou des recherches statistiques etendues le probleme de l enseignement de l allergologie doit etre resolu

Cet enseignement devrait comporter deux echelons 1° l organisation de cours d allergologie clinique pour les etudiants frequentant les hopitaux et 2° la creation d un enseignement post universitaire s adressant plus specialement aux medecins diplomes

Ces deux cycles d enseignement devraient etre exclusivement d ordre *pratique* comporter un minimum de conferences ex cathedra un maximum de mises au point et de discussions au cours de presentations de malades

Malheureusement une telle organisation semble etre difficile a mettre sur pied à l heure actuelle sur le plan local C est pourquoi nous reprenons la proposition jadis emise qu un groupement international tel l Academie Europeenne d Allergologie fonde dans plusieurs villes universitaires des centres d enseignement post universitaire bases sur les diverses communautes linguistiques de l Europe

La Faculte de Medecine de Paris grâce à son experience deja longue des cours de perfectionnement en allergologie grâce à la haute qualite de son corps professoral à sa situation geographique favorable aux facilites qu elle peut offrir aux etudiants semble etre tout indiquee pour dispenser un tel enseignement aux medecins de langue française soit en developpant ce qui existe deja soit en creant de toute piece sur le modele des universités americaines une session academique durant les mois de l ete

La Societe Belge d Allergie envisagerait en outre avec faveur qu un autre centre poursuivant les memes buts soit organise en Hollande au benefice des medecins belges dont le flamand est la langue usuelle

RÉSUMÉ

Divers aspects medico sociaux des maladies allergiques en Belgique ont ete passes en revue

Au point de vue social l asthme est certainement l affection allergique la plus repandue et la plus grave Son taux de mortalite depasse celui de la tuberculose et le cout de la maladie (chomage et soins medico pharmaceutiques) peut etre evalue a 1 835 millions de francs B ou $ 3 671 680 par an dont la majeure partie est a charge de la Securite Sociale c est a dire de la collectivité

Il n existe aucune chaire d allergologie dans les facultes de medecine ni aucun service hospitalier specialise Quelques médecins ont creé à titre souvent precaire des consultations externes pour malades allergiques dans le cadre des consultations specialisees qui existaient déjà

Les besoins les plus urgents a satisfaire comprennent

1 Organisation d un enseignement universitaire et post universitaire surtout d ordre pratique

2 Creation d un armement medico social de protection de l enfance contre l asthme et les maladies connexes

3 Intervention plus equitable de la Sécurité Sociale pour tout ce qui concerne les soins médico pharmaceutiques immediats aux malades allergiques

4 Aide financiere de la Securité Sociale visant à etablir une ... prevention des maladies allergiques respiratoires

SUMMARY

Various medical and social aspects of the allergic diseases in Belgium have been reviewed

From the social point of view asthma is undoubtedly the most frequent and the severest one among allergic diseases It s mortality rate is higher than the rate of tuberculosis and the expenses involved (Dole Medical and Pharmaceutical cares) run into 1 milliard 835 millions Belgian franks which means 3 671 680 U S A dollars per year the major part of the expenses are supported by the Health Services that is to say the collectivity

Our faculties have no allergological chairs and our hospitals no specialized departments

A few physicians have created in hospitals and sometimes precariously joined to already existing specialized out patients departments some allergic medical advising departments for patients from the outside

Our most urgent needs are

I The foundation of a mostly practical universitary and post graduated allergological tuition

II To have at our command medical and social weapons in order to enable us to protect childhood against asthma and related diseases

III An uprighter treatment and understanding on the part of the health services for everything in connection with immediate medical and pharmaceutical care for allergic patients

IV *Financial support from the Health Services to the purpose of initiating a policy for the prevention of allergic diseases*

ZUSAMMENFASSUNG

Zahlreiche medizinische und soziale Aspekte allergischer Erkrankungen wurden in Belgien besprochen

Vom sozialen Standpunkt aus geschen ist zweifellos Asthma die haufigste und schwerste der allergischen Erkrankungen Seine Mortalitatsquote ist hoher als die bei Tuberkulose und die Kosten (Spende medisinische und pharmazeutische Pflege) die dadurch bedingt werden betragen 1 milliard 835 millione belgische Franken was 3 671 680 E S Dollars pro Jahr bedeutet der grosste Teil dieser Ausgaben werden vom Gesundheitswesen getragen das heisst von der Allgemeinheit

Unsere Fakultaten haben keine Lehrstulle fur Allergologie und unsere Krankenhauser keine spezialisierten Abteilungen

Eine gewisse Anzahl von Arzten grundete manchmal nur widerruflich und mit schon vorhandenen spezialisierten Abteilungen gekeppelt einige medizinische Allergieambulanzen fur von Aussen kommende Patienten

Die dringlichsten Notwendigkeiten fur uns sind

1 Die Grundung einer zum Grossteil praktisch ausgerichteten Universitats und nach der Graduation Allergologieausbildung

2 Medizinische und soziale Waffen die es uns ermoglichen die Kindheit vor Asthma und demit verbundenen Erkrankungen zu schutzen sollen uns zur Verfugung stehen

3 Grundlichere Behandlung und aufrichtigeres Verstandnis von Seiten der Gesundheitsorganisationen fur alles was mit einer unmittelbaren medizinischen und pharmaceutischen Obhut allergischer Patienten zusammenhangt

4 Finanzielle Unterstutzung vom Gesundheitswesen zur Verwircklichung der zur Veruhtung allergischer Krankheiten notigen Anstalten

RESUMEN

Se pasan en revista diversos aspectos médico sociales de las enfermedades alergicas en Bélgica

Desde el punto de vista social el asma es ciertamente la afeccion alergica más extendida y la mas grave La tasa de mortalidad es mayor que la de la tuberculosis y el costo de la enfermedad (ausentismo y atencion medico farmacéutica) puede ser calculado en 1 835 millones anuales de francos belgas de los cuales la mayor parte es financiada por la *Securité Sociale* es decir la colectividad

No existe ninguna cátedra de alergología en las Facultades de Medicina ni tampoco ningun servicio hospitalario especializado Algunos profesionales han formado de manera precaria a menudo consultorios externos para los enfermos alergicos dentro de los consulto ios especializados ya existentes

Las necesidades más urgentes a satisfacer comp enden

1 La organizacion de la ensenanza universitaria y post universitaria sobre todo de carácter práctico

2 La creación de un equipo medico social de proteccion a la infancia contra el asma y las enfermedades conexas

3 La intervención mas justa de la *Securite So iale* en todo lo que concierne a la atención médico farmaceutica inmediat de los enfermos alergicos

4 Ayuda financiera de la *Sécurite So iale* con el fin de establecer una politica de prevencion de las enfermedades alergicas respiratorias

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FINLAND

by

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Finland situated between latitudes 60 and 70 is the most northerly country in the world with the exception of Iceland One third of Finland s area lies in the Polar Circle It is a land of great forests and boasts of 60 000 lakes and 30 000 islands The lack of high mountains make the country well suited for agriculture A big part of its 4 million people are farmers and are scattered over a great area The population density being only 1.7 inhabitants per square kilometer

The cold long and severe winters with the lack of sunshine and vitamin C predisposes its inhabitants to infections that are difficult to conquer It also makes bronchial asthma the most common allergic disease The necessity of warm and heavy clothing causes skin diseases to be next in prevalence among both children and adults Allergic rhinitis due to chronic infections in the upper respiratory tract is often seen Hayfever caused by pollen from timothy flowers and trees is a minor form of allergy This is due to the short summer season The huge forests dividing the fields also prevent the pollen from spreading over great areas

The occurence of allergy as a whole is greater in the part of the country near the seashore and around the big lakes A study of the occurence of allergy in about 5 000 Finnish school children in the western part of the country near the coast gave the figure of 6 81 % An investigation of 28 000 school children of the same age in Helsinki the capital of Finland showed the incidence of 3 6 % The frequency of skin diseases was in the first mentioned material 5 2 % in the latter only 2 1 % that of bronchial asthma 0 6 % and respiratory 0 7 % Other allergies counted for 1 % in the first 0 8 % in the latter material

In 1954 the Finnish army rejected 0 96 % of the recruits 18 years of age because of bronchial asthma This figure is in close conformity with the 0 9 % stated by Williams as cause of rejection from the armed forces in the 18 year old group and the 0 9 % incidence of asthma in the adult population in England and Wales in 1944 47 It also conforms with the 0 94 % figure on bronchial asthma given by *et al* Collins among the white population in Baltimore in 1939 43

A *sexual* difference in the occurrence of distribution of allergic diseases was clearly revealed in our studies The incidence of bronchial asthma and the combination of asthma and eczema was higher in boys that of eczema in girls The boys symptoms of allergy be it asthma or eczema were seen at an earlier age than in girls Also in adults up to 40 years of age the same tendency was noticed The incidence of bronchial asthma was greater in men, that of eczema in women After the age of 40 no sexual difference in the distribution of allergic diseases was seen

THE CAUSES OF ALLERGY

Chronic infections in different parts of the body mainly in the upper and lower respiratory tract are the most common causes of allergy in Finland Infections in sinuses tonsils and teeth are mostly seen Out of 500 asthmatic children treated in the wards of the Finnish allergy hospital 88 % showed chronic infections of the upper 62 % of the lower respiratory tract In only 12 % of the children no focal infection could be found 200 adult hospital patients suffering from bronchial asthma were x rayed and examined by the otolaryngologist and dentist In 72 % sinusitis was found being in 21 5 % of a Pansinusitis 18 5 % had polyps 20 % chronic tonsillitis and 58 % periapical infections of the teeth In only 10 % of the studied material no signs of chronic infection could be found In the infected cases it was clinically established that a definite and lasting improvement of the asthma was seen only in cases in which a sanitation of foci of infection could be performed

In spite of the great importance of chronic infection as cause of allergy in our country allergy to extrinsic factors such as inhalants and food is not uncommon In the material mentioned above 36 % of the patients with chronic infections showed marked positive skin tests to other allergens but bacteria It is often difficult to determine which of these factors is the primary

In the inhalant group dust mostly house dust is the most prominent cause of allergy both in adults and in children next to it comes horse and cows hair Sometimes the combined sensitivity to cows hair cowsmilk and meat is seen giving manifestations of both asthma and eczema in the same person Sheep wool causes an often seen sensitivity This is due to sheepskin and using of woollen material in clothing and handicrafts Almost everybody in the rural areas wears home knitted woollen stockings and hand knitted or woven woollen clothes and also blankets Often hand woven rugs from wool and cows hair cover floors and walls These people may be *sensitive even to lanolin (sheep fat) in the ointments* used for eczemas Feather also is a rather common cause of allergy It is seen not only among owners of poultry farms but also among people sleeping on feather mattresses

Food allergy is the most common form of allergy in small children whereas it is not often seen in adults Hypersensitivity to milk is mostly observed next comes eggs chocolate fish wheat and peas As to pollens hypersensitivity to timothy is the most common Allergy to birch pollen is not often seen but is very intensive while it lasts which is usually abou 10 to

12 days Hypersensitivity to other trees and flowers is occasionally observed mostly in gardeness or owners of flower shops

Hypersensitivity to drugs has been more and more observed during recent years Anaphylactic shock due to penicillin occured few times Two fatal cases have been reported in our country In 1 000 allergic patients intracutaneous skin tests with penicillin were positive in 33 % Same percentage was revealed in adults and children

A specific study of fungi as cause of allergy has not been performed in our country Clinical experience suggests that many eczemas in adults and children are caused by fungi

DIAGNOSIS

At the Hospital for Allergic Diseases in Helsinki as a routine 40 intracutaneous tests are performed on the upper arms of the patients Further intracutaneous passive transfer scratch patch food inhalant trial and Leucopenic Index tests are used individually when found necessary The extracts are prepared in the laboratory of the hospital by the Coca method They are standardized biologically according to suggestions made by the Extract Committee of the Scandanavian Allergy Society Tests with bacterial extracts have been abandoned during the last years becau e of the inadequate results obtained A thorough search for foci of infections is performed In addition special attention is paid to hormonal and metabolic disturbances which may have changed the organism of the patient from a normal to an allergic For this purpose Kepler glucose and insulin tolerance tests and determinations of hormones and minerals are performed

TREATMENT

The aim of our therapy is to alleviate the patient from existing allergic symptoms and correct disturbances found in the organism in order to facilitate the rechange from an allergic to a normal state or at least from manifest to latent allergy

The antiinfections treatment includes focal sanitation combined with use of antibiotics stock or autovaccines and gammaglobulin

Specific hyposensitization is used in cases with positive skin tests After titration of the degree of sensitization treatment is started as a *preseasonal rush treatment* with injections given every 3 to 4 hours When the highest tolerated dosage is reached the same dose is repeated as maintenance treatment once a month for 2 to 3 years In cases of food allergy hyposensitization *per os* is preferred

This specific treatment is combined with *unspecific* such as sulfur in oil and histaminazo protein injections and electroaerosol therapy

The *general treatment* perposes to correct hormonal metabolic and psychic disturbances found Patients showing an insufficiency of the carbohydrate metabolism are given a special diet It contains a minor of carbohydrates and an increase of proteins fats and vitamins especially C vitamins Intervals between meals should be not more than four hours in order to maintain an even bloodsugar level

After the patients have finished the treatment in the hospital specially trained allergy nurses are keeping up the contact with them through home visits and correspondance

PROFESSIONAL AND EDUCATIONAL TRAINING

In 1934 the first Finnish allergy clinic was opened at the University hospital for internal medicine in Helsinki It was headed by a pediatrician with one year training in allergy in U S A In 1947 the allergy work was concentrated in the Hospital for Allergic Diseases a hospital entirely devoted to allergy maintained by the Finnish Foundation for Allergological Research In 1951 the chief physician of the hospital was appointed assistant professor of allergy at the University of Helsinki From this time one teaching of allergy has been given to the medical students and doctors have had opportunity of specializing in this field Allergy is a sub specialty of internal medicine or pediatrics Two years of work in an allergy clinic are required for specializing

Three pediatricians are now specialists in allergy About 60 physicians have received 1/2 to 1 year training at the allergy hospital and are in different parts of the country cooperating with the hospital

The people in Finland have given great understanding and gratitude to the allergy work performed

Also specialists in other fields of medicine seem to show an increased appreciation for this work

SUMMARY

The most common allergies in Finland are bronchial asthma and various skin diseases Bronchial asthma and the combination asthma and eczema are more often seen in males In females up to 40 years of age allergy of the skin is more common Allergic symptoms in boys develope at an earlier age than in girls After 40 no sexual difference in the distribution of allergy was found

Infections in the upper and lower respiratory tract are the main cause of allergy Of 500 asthmatic children 88 p 100 showed chronic infections of the upper and 62 p 100 of the lower respiratory tract Otolaryngologic and X ray studies of 200 adult asthmatics revealed sinusitis in 7- p 100 (in 21 5 p 100 pansinusitis) 18 5 p 100 had polyps 20 p 100 chronic tonsillitis and 58 p 100 periapical infection 36 p 100 also showed marked skinreactions to other allergens

In adults sensitivity to housedust horse hair cow hair and sheep wool are most common Food allergy (milk egg wheat) is more frequently seen in small children

Hayfever is not common It is mostly cau ed by pollen from timothy and birches

Drug allergy specially due to penicillin is often seen

Diagnosis Thorough search for foci of infection Attention paid to hormonal and metabolic disturbances specially in suprarenal cortex and

sugar metabolism (Kepler glucose and insulin tolerance tests determination of hormones and minerals) Routine 40 intracutaneous and necessary individual scratch patch and passive transfer tests Food and inhalant exposure and Leucopenic Index

Treatment Focal sanitation antibiotics stock and autovaccine and gammaglobulin Specific hyposensitization as rush treatment (up to 15 injections per day) after titration of degree of sensitivity Maintenance treatment once a month for 2 3 years Food hyposensitization per os Antihistamines sulphur in oil and electroaerosol treatment *Correction of* hormonal metabolic and psychic disturbances Diet reduction of carbohydrates increase of protein fat and C vitamins four hour interval between meals

Educational training In 1934 first Allergy Clinic started In 1946 a special hospital for treatment of every kind of allergy was opened by the Finnish Foundation for Allergological Research In 1951 Assistant Professorship of Allergy installed at the University of Helsinki Medical School Allergy is a subspecialty of pediatrics or internal medicine After specializing in one of these fields 2 years of training in an allergy clinic is required

RÉSUMÉ

L asthme bronchique et diverses affections cutanees sont les maladies allergiques les plus courantes en Finlande On rencontre plus souvent chez les hommes l asthme et l eczema combinés Jusqu à la quarantaine l allergie cutanée est plus commune chez les femmes

Les manifestations allergiques se produisent plus tot chez les garçons que chez les filles ' Apres quarante ans l âge ne joue plus de role dans la répartition des maladies allergiques

Les infections des voies respiratoires inférieures ou superieures sont les principales causes d allergie Sur 500 enfants asthmatiques 88 p 100 presentaient des infections chroniques des voies respiratoires superieures et 62 p 100 des voies respiratoires inférieures

L examen oto rhino-laryngologique et par rayons X de 200 asthmatiques adultes a permis le dénombrement suivant 72 p 100 de cas de sinusite (dont 21 5 p 100 de pansinusites) 18 5 p 100 de polypes 20 p 100 d amygdalites chroniques et 58 p 100 d infections périapicales 36 p 100 des malades examines ont accuse des reactions cutanées *tres nettes a d autres allergenes*

Chez les adultes les sensibilisations aux poussieres domestiques et aux squames de cheval aux poils de vache et de mouton sont les plus frequents On rencontre les allergies alimentaires (lait œufs blé) le plus souvent chez les jeunes enfants Le rhume des foins est rare Il est principalement imputable aux bouleaux et à la fleole des prés *(Phleum pratense)* Les cas d allergie à la penicilline sont fréquents

Diagnostic Recherche sérieuse des foyers d infection Prise en considération des troubles d origine hormonale et metabolique plus particulièrement du cortex surrenalien et pour le métabolisme du sucre (Test de Kepler

de la tolérance du glucose et de l insuline détermination des substances hormonales et minérales)

Méthodes couramment employées 40 tests intradermiques (nécessairement individuels) par cutiréactions épidermo réactions transfert passif exposition aux inhalants et aux aliments index leucopenique

Thérapeutique Traitement des foyers de la maladie antibiotiques stock vaccins auto vaccins gamma globuline

Désensibilisation spécifique comme traitement d urgence (jusqu a 15 injections par jour) après évaluation préalable du taux de sensibilisation Traitement d entretien pendant deux ou trois ans

Désensibilisation aux aliments per os Antihistaminiques suspension de soufre dans l huile traitement par électro aerosols Correction des troubles hormonaux métaboliques et psychiques

Régime alimentaire Diminution des hydrates de carbone augmentation des protéines des graisses et de la vitamine C Repas pris a quatre heures d intervalle

Enseignement allergologique Les débuts de la première clinique allergologique datent de 1934 En 1946 la Fondation Finlandaise pour la Recherche Allergologique a ouvert un hopital pour le traitement de toutes les maladies allergiques En 1951 une chaire de Professeur Agrégé d Allergie a été créée a l École de Médecine de l Université d Helsinki

L allergologie est considérée comme une branche specialisée soit de la médecine interne soit de la pédiatrie Après une spécialisation dans l une de ces disciplines les allergologues doivent faire deux ans d etudes dans une clinique allergologique spécialisée

ZUSAMMENFASSUNG

Die haufigsten Allergien in Finland sind Bronchialasthma und verschiedene Hauterkrankungen Bronchialasthma und die Kombination Asthma mit Ekzem werden bei Mannern haufiger beobachtet Bei Frauen bis zu 40 Jahren werden Hautallergien ofters gesehen Allergische Symptome treten bei den Jungen in einem fruheren Alter auf als bei Madchen Nach dem 40 Lebensjahr konnten keine Unterschiede in der Allergieverteilung bei Mannern und Frauen gefunden werden

Infektionen des oberen und unteren Respirationstraktes sind die hauptsachlichen Ursachen der Allergie Von 500 asthmaleidenden Kindern zeigten 88 p 100 chronische Infektionen des oberen und 6. p 100 des unteren Respirationstraktes Otolaryngologische Untersuchungen und [illegible] ergaben in 72 p 100 [illegible] isenpolypen, [illegible] periapikale [illegible] Entzundungen 36 p 100 zeigten auch deutliche Hautreaktionen gegenuber anderen Allergenen

Bei Erwachsenen ist eine Ueberempfindlichkeit gegen hauslichen Staub Pferdehaaren Kuhhaaren und Schafwolle am meisten verbreitet Eine Lebensmittelallergie (Milch Eier Weizen) kommt bei kleinen Kindern haufiger vor

Heufieber ist nicht sehr verbreitet Es wird meist von Birken und Timotheenbluten verursacht

Eine Medikamentenallergie besonders gegenuber Penicillin wird oft beobachtet

Diagnose Grundliche Untersuchung auf Foci und Infektionen hin Hormon und Stoffwechselstorungen besonders des Nebennierenrinden system und des Zuckerstoffwechsel sollen beachtet werden (Kepler Glukose und Insulintoleranztest Hormon und Mineralbestimmung) 40 intrakutane Routinetests und Kutanproben besondere Epikutan proben und Passiv Transfer Tests Nahrungsmittel und Inhalations exposition und weisses Blutbild

Behandlung Focus Sanierung Antibiotika Stamm und Autovaccine Gammaglobuline Spezifische Hyposensibilisierung als Hauptbehandlung (bis zu 15 Injektionen pro Tag) nachdem man den Grad der Ueberempfind lichkeit titriert hat. Dauerbehandlung einmal im Monat durch 2 3 Jahre Nahrungsmittel desensibilisierung per os Antihistamine Schwefel in Ölsuspension Elektroaerosoltherapie Ausgleichen von hormonellen stoffwechselbedingten und psychischen Storungen Diat Verminderung von Zucker Vermehrung von Proteinen Fette und Vitamin C Vierstun denintervalle zwischen den Mahlzeiten

Ausbildung 1934 wurde die erste Allergieklinik gegrundet 1946 wurde von der finnischen Gesellschaft fur Allergologieforschung ein Spezialkran kenhaus zur Behandlung aller Arten von Allergien gegrundet 1951 wurde ein Lehrstuhl fur einen ausserordentlichen Professor fur Allergie an der medizinischen Fakultat der Universitat Helsinki eingerichtet Allergie ist eine Subspezialitat der Kinderheilkunde oder Inneren Medizin Es werden 2 Jahre Tatigkeit an einer Allergie Klinik nach der Spezialisierung in einem dieser Facher verlangt

RESUMEN

Las enfermedades alergicas más comunes en Finlandia son el asma bron quial y algunas afecciones de la piel El asma bronquial y su asociacion con el eczema se observa más frecuentemente en los hombres En las mujeres hasta los 40 años es mas comun la alergia dermatológica Los sintomas alérgicos se desarrollan más precozmente en los niños que en las niñas Despues de los 40 anos de edad no se observan diferencias en la distribución de las alergias en hombres y mujeres

Las infecciones del árbol respiratorio constituyen la principal causa de la alergia Sobre 400 ninos asmaticos el 88 p 100 tenía infecciones crónicas del árbol respiratorio superior y el 62 p 100 del inferior Exámenes otorri nolaringológicos y de rayos X efectuados sobre 200 asmáticos adultos indicaron sinusitis en el 72 p 100 de los casos (pansinusitis en el 21 5) polipos en el 18 5 p 100 amigdalitis crónica en el 20 p 100 e infecciones perapicales en el 58 p 100 En el 36 p 100 de los enfermos se obtuvieron reacciones cutáneas a diversos alergenos

En los adultos es frecuente la sensibilización a polvo domestico pelos de caballo y vaca y lana La alergia alimenticia (leche huevo trigo) se ve más a menudo en los niños pequeños

La fiebre de heno es rara y es provocada sobretodo por el polen de abeto y gramíneas (Phleum)

La alergia a drogas causada por la penicilina se encuentra a menudo

Diagnostico Se realiza una cuidadosa busqueda de focos sépticos Se presta mucha atención a los trastornos hormonales y metabólicos, especialmente de las suprarrenales y del metabolismo de la glucosa (Kepler tests de tolerancia de la insulina dosificación de hormonas y minerales) Se efectuan unos 40 *tests* intradérmicos de rutina y los que sean además necesarios en cada caso ya sea por cutirreacción prueba de parche de transferencia pasiva de provocacion con alimentos o inhalantes e índice leucopénico

Tratamiento Eliminación de los focos septicos antibióticos stock y autovacunas gamaglobulina La desensibilización específica por el metodo «rush» (hasta 15 inyecciones diarias) luego de determinar el grado de sensibilidad del paciente Tratamientos de mantenimiento con una inyeccion mensual durante 2 o 3 años Desensibilización alimenticia por boca Antihistamínicos azufre coloidal tratamiento por aeroelectrosoles Correccion de los trastornos hormonales metabólicos y psíquicos Dietas de reducción de hidratos de carbono y aumento de proteínas grasas y vitamina C e intervalos de 4 horas entre las comidas

Aspectos educacionales En 1934 se instaló la primer clínica de alergia En 1946 la Fundación Finlandesa de Investigaciones Alergológicas inauguró un hospital dedicado especialmente a las enfermedades alérgicas de todo tipo En 1951 fué creado un cargo de Profesor Asistente de Alergia en la Universidad de Helsinki La alergia es una subespecialidad de la medicina interna o de la pediatría y se requiere primeramente la especialización en algunas de esas ramas y luego 2 años de práctica en una clinica alérgica

CUBA

por

G ESTRADA DE LA RIVA [illegible]

[illegible] (Habana, Cuba)

La reaccion inmuno biológica alérgica es un fenómeno [illegible] ya ocurra en Cuba o en cualquier otro lugar de la Tierra. No [illegible] determinadas condiciones climatológicas, geográficas [illegible] y hasta [illegible] del habitante de Cuba conducen a la observación de [illegible] tanto etiologicas como clínicas que se apartan [illegible] del [illegible] habitual de producirse el fenómeno alérgico.

La situacion geográfica de Cuba entre los paralelos 20 y 23 N y los meridianos 74 y 85 E aproximadamente la sitúa en la zona [illegible] proxima a la templada del norte determinando esta situación un clima benigno con pocas variaciones entre sus estaciones [illegible] de lluvias que coincide con parte de la primavera y el verano y [illegible] que comprende la mayor parte de nuestro invierno tras la [illegible] que se extiende de principios de septiembre a noviembre. Las temperaturas fluctuan entre 35° C en la época estival y 18 C en el invierno [illegible] descensos a 15° C.

La distribución orografica de Cuba desprovista de grandes elevaciones [illegible] oriental de la isla y su situacion entre el Mar [illegible]

fenca sobre toda su area [illegible] relativa que fluctuan entre 64 y 76 por ciento en la estación seca y entre [illegible] por ciento en la estación de las lluvias.

Todos los factores expuestos hacen de Cuba una reg[illegible] siendo esporád[illegible] es un agente alergénico de excepción. Esos mismos factores [illegible] vados de esta modalidad etiológica [illegible] una vasta flora micótica ambie[illegible] favorecer el desarrollo de [illegible] las mayores concentraciones durante la época de lluvias.

Es el bio organismo micótico junto al «complejo polvo de casa» el elemento etiológico en el más alto numero de casos de alergia respiratoria de carácter exógeno en nuestro medio

Paralelamente y en mayor grado corren las estadísticas de alergia respiratoria de carácter bacteriano comprendiendo al igual que en los grupos anteriores toda la sindromología del aparato respiratorio desde la simple tos alérgica hasta el más profundo cuadro de asma bronquial pasando por nutridas casuísticas de bronquitis bronquiectasias rinitis *sinusitis y hasta ocasionales casos de consolidación pulmonar a tipo Loeffler*

En orden de menor frecuencia son observados grupos de alergia respiratoria de carácter exógeno por sensibilización a epidérmicos de animales y productos misceláneos del medio y en menor grado por sensibilización a alimentos especialmente en adultos



Las dermatosis constituyen el segundo gran grupo de alergias en nuestro país especialmente las del tipo reaccional retardado por sensibilización de la epidermis las dermatitis por contacto

Siendo la población de Cuba eminentemente agrícola e industrial y hallándose notablemente concentrada esta actividad en la industria azucarera no es de extrañar que sea en el obrero del azucar donde hallamos los grupos mas nutridos de esta forma clínica de la alergia

Se hallan especialmente afectados los cultivadores de la caña de azucar por su exposición constante durante varios meses del año al contacto de oleoresinas del tallo de la flor o guin principal vector de sustancias *volátiles las hojas y la caña misma siendo frecuente la observación durante* los meses de diciembre a mayo de numerosos casos de dermatitis de la más variada distribución anatómica pero con especial localización en la región palmar izquierda por prensión de la caña al ser cortada y ambas piernas por contacto de las hojas inferiores y región externa de ambos brazos La cara como fenómeno de curiosa observación es rara vez afectada Posiblemente ello sea debido a la protección conferida por los sombreros de anchas alas de los agricultores

El segundo factor determinante en orden de frecuencia de nuestras dermatitis contactantes son los productos químicos muy especialmente los contenidos en cosméticos Cuba es un país altamente *consumidor* de productos cosmeticos y es sabido que la mayoría de los manufactureros sacrifican la inocuidad de los ingredientes a las cualidades adherentes y *lucimiento de sus productos siendo como es natural* los más frecuentes ofensores los esmaltes para uñas lociones y tintes para el pelo y demás integrantes del maquillaje femenino



El tercer grupo de las alergias *observadas en Cuba* está constituído por sensibilizaciones de la piel en su aspecto profundo donde el mecanismo patogenico se halla constituído por intensas vasodilataciones en las capas

inferiores del dermis con actividad de sustancias histaminoides o serotonina dando lugar a estados de urticaria propiamente dicha o del tipo gigante angioedema y edema angioneurótico y urticarias papulosas y prurigo simple constituyendo el grupo de los «liquen urticatus»

En la mayoría de los casos el agente sensibilizante en este tipo de dermosis es de nuevo el producto químico pero por vía ingestante o inyectante y en la forma de agentes medicamentosos alergia a drogas En este grupo se hallan comprendidos la enfermedad del suero gran diversidad de cuadros anafilactoides y verdaderos estados de asma bronquial y rinitis como parte de los ultimos

Si bien aunque en menor grado los alimentos y elementos larvarios y productos del catabolismo de parasitos intestinales son factores etiológicos importantes en la producción de dermatitis urticantes son las drogas los agentes ofensores más frecuentemente observados en las dermatosis referidas así como en numerosos casos de dermatitis eczematoides muy similares a verdaderos cuadros de dermatitis atópica eritemas generalizados y multiformes reacciones acneiformes y excepcionalmente purpura simple no-trombocitopénica Como en todas partes son los ioduros bromuros salicilatos fenolftaleína sulfonamidas y penicilina los agentes mas frecuentes en este tipo de sensibilización

En Cuba como en todos los países tropicales es frecuente el parasitismo intestinal especialmente en las regiones rurales Como hemos señalado anteriormente los elementos larvarios de los parásitos sus productos catabólicos y aun su soma proteico constituyen potencialmente alergenos endógenos que dan lugar a numerosas formas clínicas de alergia ocupando el primer lugar en orden de frecuencia las dermatitis urticantes para ser seguidas por diversos tipos de dermatosis eczematoides repercusiones en el aparato respiratorio y con menor frecuencia alteraciones del colágeno con cuadros clínicos de sindrome de Loeffler eosinofilia tropical lupus eritematoso diseminado dermatomiositis y periarteritis nodosa sin omitir algunos aspectos de artritis reumatoide



En el aspecto social cabe a Cuba el privilegio de hallarse junto a los primeros países que reconocieron la alergología como especialidad medica autónoma Gestiones realizadas por el autor ante el Colegio Medico Nacional y el Ministerio del Trabajo de Cuba lo dejaron así establecido y a ese tenor fué creado y establecido el primer servicio médico social de alergia en este país en la Casa de Salud de la Asociacion Canaria en La Habana bajo la organización y dirección actual del autor En 1944 fué creado el Servicio de Investigaciones Alergicas del Consejo Nacional de Tuberculosis adscrito al Ministerio de Salubridad organizado por su actual director Doctor José M Quintero Fossas Más tarde fué establecido un servicio dedicado a la especialidad en el Hospital Calixto García actualmente Hospital Universitario y posteriormente han sido creados servicios especializados de alergología en hospitales como los del Ejército Constitucional y Policía Nacional y numerosas clínicas privadas

La enseñanza de esta disciplina fué establecida desde 1938 por el autor

en la Cátedra de Patología Experimental de la Escuela de Medicina en la Universidad de La Habana Posteriormente fue creada la Cátedra de Alergia Clínica para post graduados en la Escuela de Verano de la Universidad Nacional Inaugurada en 1945 fué el autor su titular en los cursos de 1945 y 1946 siendo posteriormente desempeñada por el actual titular Doctor Quintero Fossas

Desde 1948 fué fundada la Sociedad Cubana de Alergia por un grupo de médicos cubanos que doce años atras habían dedicado a esta especialidad toda su capacidad profesional Cadrecha de los Santos Pedrera Quintero Fossas y el *autor son algunos de aquel grupo fundador Inmediatamente* fué incorporada a la Asociación Internacional de Alergistas precursora a la celebrante de este congreso cuyo nombre y estructuración actual surgieron en el I Congreso Internacional de Alergología Zurich Suiza 1951 en el que la Republica de Cuba estuvo representada por misión oficial

RÉSUMÉ

L auteur s occupe des caractéristiques géographiques et climatiques de Cuba et de ses conséquences sur les types prédominants d allergenes

Les agents étiologiques les plus fréquents dans les allergies respiratoires sont les champignons et la poussiere Il y a aussi un grand nombre de cas d allergie du type bactérien Les squames et autres inhalants ont une moindre importance et moins encore les aliments surtout chez les adultes

Les dermatoses constituent le deuxieme grand groupe d allergies en particulier les dermatites par contact produites par la canne a sucre et les cosmétiques

Un troisieme groupe d allergies est formé par les sensibilisations de la peau telles que les urticaires et œdemes angioneurotiques provoques principalement par les médicaments

L auteur considere brievement les aspects sociaux et l enseignement dans son pays

SUMMARY

The author reports on the geographical and climatic features of Cuba and on their incidences on the main allergens

The most common etiologic agents in respiratory allergy are moulds and dusts Many cases of bacterial allergies are also encountered Danders and other inhalants play a smaller part and foods specially in adults are even less important factors

The skin diseases form the second large group of allergic diseases parti

angioedema

The author briefly deals with social aspects of the question and with the allergical tuition in his country

ZUSAMMENFASSUNG

Der Autor beschaftigt sich mit den geographischen und klimatischen Merkamalen von Kuba und deren Bedeutungen fur die wichtigsten Allergentypen

Die atiologisch am haufigsten anzutreffenden Stoffe sind bei den Allergien des Respirationstraktes die Pilze und der Staub Es gibt auch eine grossere Zahl von Allergiefallen des bakteriellen Typus Schuppen und andere Inhalantia sind von geringerer Bedeutung noch weniger bedeutend sind die Nahrungsmittel besonders bei den Erwachsenen.

Die Dermatosen stellen die zweite grosse Gruppe von Allergien dar besonders die Dermatitiden durch Kontakt mit Rohrzucker und Kosmetika

Eine dritte Allergiegruppe stellen die Sensibilisierungen der Haut in Form von hauptsachlich durch Medikamenten bedingten Urticaria Angioödemen und angioneurotischen Ödemen dar

Der Autor geht kurz auf soziale Aspekte und den Unterricht in seinem Lande ein

RESUMEN

El autor se refiere a las características geograficas y climáticas de Cuba y a sus consecuencias sobre el tipo de alergenos predominantes

Los agentes etiológicos más frecuentes en las alergias respiratorias son los hongos ambientales y el polvo domestico existiendo asimismo un elevado numero de casos de alergias de tipo bacteriano Los epitelios y otros inhalantes se observan con menor frecuencia y menos aun los alimentos especialmente en adultos

Las dermatosis constituyen el segundo gran grupo de alergias en especial las dermatitis de contacto provocadas por la caña de azucar y los cosmeticos

Un tercer grupo de alergias está constituido por sensibilizaciones de la piel del tipo de urticarias angioedema y edema angioneurotico debidas principalmente a agentes químicos

El autor se refiere brevemente a los aspectos social y docente de la alergologia en su país

ISRAEL

by

M J GUTMANN M D

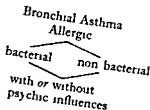
(Rothschild Hadassah University Hospital Jerusalem)

The chief problem which occupies us here is the interaction of geographical climatic influences (sirocco khamsin sharav) (1 2) some specific infections (Leishmaniasis) and the adaptation of the immense number of immigrants in the country The Jewish population of Israel had doubled within three years from 650 000 in mid 1948 to 1 300 000 in mid 1951 At the end of 1957 it had almost trebled since 1948 and the total population has almost reached two millions (3) So far we know of only one special case of an epidemic of bronchial asthma due to adaptation difficulties (4 a and b)

I TYPES OF BRONCHIAL ASTHMA

We differentiate our allergic cases as bacterial and non bacterial forms (fungi pollen etc) and mixed forms which may be *or* not be under the influence of psychic factors

Here is the scheme



There are no particular allergic diseases characteristic of the country

II INCIDENCE OF ASTHMA

No statistically reliable figures of cases of bronchial asthma exist in this or any other country For several years we have been working on such statistics Among a sample of 10 443 people in different parts of the country

comprising 1 690 families we found 139 asthmatics that is to say 1,3 p 100 of the whole population

Most striking is the great incidence of asthmatic children We have sought an explanation but as yet none of those suggested has been able to stand up under criticism

III CAUSES

As a result of examinations repeated last year of 400 cases of bronchial asthma the following causes have been found as definitely responsible for attacks in every individual case but more than one cause may play a role in some patients These cases represent patients from all parts of the country not only Jerusalem but the various causes are not evenly distributed among all parts of the country

1	Fungi		55 5 %
2	a) Bacterial allergens	18 5	
	b) Infections (upper respiratory tract)	22 5	41 0
3	Pollen		13 0
4	Food		18 5
5	Drugs		2 5
6	Psychic factors		12 5
7	Other factors		2 5

Now, some details on the different causes of asthma

ad 1 FUNGI The most important fungi are

Alternaria
Hormodendrum and Cladisporium
Penicillium
Aspergillus
Monilia
Actinomycetes
Yeasts

It is important to realize that inside fungi that is those found in houses and bedding upholstery materials etc are more important that those in the air The content of fungi in the air changes very quickly even with a slight draft (R Golan 5 and 6)) Clinically fungi play a more important role in the hot wet coastal plain This is proved by the fact that even after exclusion of psychic factors a change of milieu from the coastal plain to the mountainous parts (Jerusalem Safed Galilee) brings immediate relief to the asthmatics esp to suffering children in most cases without the need for any drugs (7) Cases with bacterial asthma (bronchitis) are mostly not relieved The material of the bedding is examined in every suspect patient If the test results are positive he is treated with the same material The bedding materials most used in this country are cotton and seagrass in the mattresses and feathers in the pillows occasionaly wool or horsehair Animal hair from rabbits and other pets are seldom used

ad 2 BACTERIAL ALLERGY AND INFECTIONS

The asthmatic disturbance in small children manifests itself with clock workklike regularity at midday the child has a running nose toward evening a somewhat sore throat and at night the wheezing characteristic of spastic bronchitis appears In reality this is a real bronchial asthmatic attack

Infections of the upper respiratory tract are the starting point Such infections frequently occur A proportion of these little patients have real bacterial allergy as is the case with adults of this type About 40 p 100 of all asthmatics are of this category

ad 3 POLLEN

There are many more cases of pollen asthma than were known several years ago They constitute about 13 p 100 of all cases of asthma But many are still not yet diagnosed they come into the clinic as asthmatics and by systematic testing pollen is recognized as the cause We know that about 40 p 100 of non treated pollen cases develop asthma of the treated only a small percentage do so But the number of pollen cases is not to be compared with the immense number in the United States here we have no ragweed and—by the way—no rhus toxicodendron To all intents the season is reduced to the months March May The most important pollens are those of grasses (Cynodon dactylon Bermuda grass) and to some extend those of olives (8 and 9)

ad 4 FOOD

We found food as the main factor in 18 p 100 of the patients some known by the patients themselves but most diagnosed by the frequently maligned skin tests These skin tests are extremely helpful especially with children The most important foodstuffs we found are

eggwhite	onion	potato
fish	soya	peanut
milk	meat	
wheat	cocoa	

In this connection the high intake of table salt is very important It acts as pacemaker in many allergic troubles Almost equally important is the starchy food (especially in times of protein shortage) since it is often a cause of meteorism resulting in physical mechanical difficulties in breathing

ad 5 DRUGS

Drugs known as cause of asthma are salicylic acid in direct or disguised form pyramidon iodine penicillin etc

ad 6 PSYCHOSOMATIC FACTORS

The scheme shown on page 1 reveals bronchial asthma with *or* without psychic factors With 12 5 p 100 of the asthmatics the psychosomatic factor was the determining factor in the clinical picture Interestingly enough in patients with real endogen psychosis we noticed an alteration of psychosis and bronchial asthma

ad 7 OTHERS

We may add that of all patients sent to this clinic with the diagnosis of bronchial asthma about 15 20 p 100 revealed other difficulties in breathing than those due to bronchial asthma

IV DIAGNOSIS

There is no country wide single method of diagnosis Here I report only my personal methods

The basis diagnostic measure is taking a thorough history of the patient *It not only indicates the direction in which we have to make special examinations* but also—if we are successful—it establishes contact with the patient This often leads not only to a good diagnosis but also to success in treatment It definitely enables us to exclude from the beginning cases of pseudoasthma as mentioned in the previous chapter The next diagnostic measure is a very thorough physical examination of the patient *x ray etc*

Skin tests We use intracutaneous tests occasionally only prick or scratch tests of which 4 6 are made at one time Usually we use a 1 p 100 or 1 per mille concentration standardized so as to allow a positive wheal reaction without causing any general reaction (Incidentally in nearly 30 years of practice we have experienced only one general reaction and this was in the *early days of allergy study*)

Preparation of extracts We prepare nearly all our extracts ourselves from the country s products and especially the patient s surroundings (bedding material house dust) My teacher Prof W Storm van Leeuwen suggested making extracts in the simplest way without changing the material too much with chemicals Pollen extracts are prepared with Glycerin *saturated salt solution (10)*

The number of extracts used is not fixed generally we make 20 30 tests in special cases the number is unlimited

Food tests we make tests with foodstuffs and these are often very helpful but we draw conclusions as to positive reactions only after a trial diet i e elimination and later restoring the suspected products to the diet (reimposition)

Bacterial extracts For many years we have used standard stock extracts The most exciting feature is that in most cases it gives immediate reactions *only occasionally delayed reactions*

Other diagnostic test materials we use are extract of liver Enteronase (histaminase)

V THERAPY SYMPTOMATIC AND SPECIFIC

[illegible] the cause eliminating the causa [illegible] the patient from the allergen [illegible] ost important measure If in any way the conditions allow it people are cooperative *in taking advice* as to exchanging bedding material changing the room or house or even the

place of residence They bring their youngsters from the wet hot coastal plain to the mountains or the dry Negev if it can be definitely proved that the new surroundings are more suitable for the patient But as is the case quite often if with the change of locality the bedding material is not likewise changed the whole measure becomes illusory

Desensitization (Hyposensitization)

We carry out desensitization by means of extracts from all positive reacting allergen extracts in slowly increased doses All treatment is carried out *intracutaneously* The many advantages of the intracutaneous method far outweigh such disadvantages as taking more time etc But we avoid general reactions At any rate I have never encountered them — The duration of treatment takes time 6 12 months in cases of allergic warm season conjunctivitis (vernal conjunctivitis) even several years

Critical notes 1 If we compare asthmatics of tender years who have had specific treatment with those who have not one thing is evident even if the treated patients are not entirely cured their general condition is very much better than that of the others

2 With increasing use of ACTH and steroid hormones by the general practitioner more and more patients interrupt their treatment looking for quicker results , or do not start at all with the specific treatment But interestingly enough the worst time seems over because patients come back asking for cure not only for temporary relief As a rule they return in a much more deteriorated state of general health

VI PROFESSIONAL AND EDUCATION

For a population of about two million we have about 4 000 physicians which gives the extraordinary proportion of one physician to 500 inhabitants but we have to take into account that more than 50 p 100 of these physicians are above 50 and they are not equally dispersed over the whole of the country

Among these 4 000 physicians there are only 7 specialists in allergy and about the same number of part time allergists In other words one out of every 600 physicians is an allergist whereas in the United States there are 1 000 allergists among 200 000 physicians that is to say one out of every 200 physicians is an allergist

But the incidence of allergists among the population is absolutely uneven For instance Kupat Holim (The Worker s Sick Fund) with a membership of about one million that is more than half of the whole population has 3 4 allergists so that it is understandable that the waiting time for allergic patients at the Kupat Holim is about six months and more

The allergists of the country and a large group of interested academicians are members of the Israel Society of Allergy The Society was founded in Jerusalem in 1949 and has today about 90 members The big majority of its members are therefore not practising allergists but biologists botanists zoologists metereologists geneticists chemists pharmacologists who are interested in allergy Many practising physicians have given us valuable clinical data

Besides the center in Jerusalem the Society has local branches in Tel Aviv and Haifa which work more or less on their own Lectures are also given

in different small cities of the country During this period of nine years altogether 38 lectures were given and 8 symposia held most of them in cooperation with other branches of the Israel Medical Organization and the Hebrew University Medical School Our activities are regularly published as Proceedings in the International Archives of Allergy and Applied Immunology (Karger Zurich and New York)

Our members have taken part as lecturers in postgraduate courses and International Congresses of Allergology but we have no teaching facilities at the Hebrew University Medical School The only official connection we have is my personal one as Consultant in Allergy to the Hadassah University Hospital in Jerusalem

There is no law stipulating qualifications for specialization but the Israel Medical Association investigates the qualifications of practitioners

VII PUBLIC ATTITUDE TOWARDS ALLERGY

We have a very allergy minded public Even many quite primitive immigrants come to the clinic with their own diagnosis allergy Morover, most of them bring their meticorten tablets with them but this happens generally when these have already lost much of their first magic and this being the reason why they come to the allergist

Jews are a people of the book and so it happens that they read much Unfortunately many journals and newspapers publish digests which simplify the science of allergy more than is good As a result the knowledge of allergy proves to be superficial and it takes much trouble to convince patients that things are not quite so simple and that without close cooperation treatment will be difficult But once this simple truth is grasped they—as already mentioned—are cooperative and prepared to make sacrificies especially for their children not only to change bedding but also rooms houses and even places of residence But of course there are limits owing to economic difficulties

Last not least in recent years we have succeeded in reducing drastically the mortality rate from bronchial asthma which, compared with that for other countries is amazingly low

D A Williams (10) for instance gives for 1930 1948 7 10 deaths from bronchial asthma in England per 100 000 population The latest figures are Holland (in 1952) 5 1 U S A (in 1952) — 4 5 (in 1954) — 3 8 New Zealand (in 1953) — 8 73 and England (in 1953) — 6 2 (11, 12 13)

In Israel the total deaths from bronchial asthma has fallen from 45 in 1951 to 22 in 1956 although in the meantime the population has risen from 1 404 392 to 1 760 000 Expressed as deaths per 100 000 population they have fallen from 3 2 in 1951 to 1 35 in 1956 (13)

Compared with deaths from asthma in other countries we find an extra ordinary small number in Israel We make this statement—for the present— without comment

Allergy knows no barriers of social status and we find it in all of its manifestations in all social groups with very little variation among them (Wittich 14) But the economic status of the patient is of the *utmost*

importance the wealthier population has more possibilities to carry out therapeutic measures We believe that it is one of our outstanding duties to improve the situation of the population as a whole

The following table presents conditions in Israel visually in headline style including the most important plus minus factors

ALLERGIC DISEASES ESPECIALLY BRONCHIAL ASTHMA IN ISRAEL

HEALTHY FACTORS (ANTI ALLERGY)

NO RAGWEED
NO RHUS TOX CODENDRON
LITTLE OCCUPATIO AL ALLE GY
D Y CLIMATE
HEALTH M NDED PUBLIC
MANY PHYS C ANS
ALLERGY M DED CO-OPERATIVE PHYSICIANS
S CK FUNDS & SOCIAL WELFARE
FEW QUACKS & HEALERS
ISRAEL SOCIETY O ALLERGY

ALLERGIC DISEASES (MORBUS LLERG CUS)

UNHEALTHY FACTORS (PRO ALLERGY)

HOT ET CL M TE
FU G
POLLE
MASS IMMIGR T O
DIFFICULT ES N ADAPT T O
SCA CITY OF LIVI G QU RTERS
PSYCHOSOM TIC FACTORS
OT ENOUGH LLERGIST
O SPEC L HOS IT DE RTMEN
NO TE CH NG FA I ITIES
NO SOC L E ICE FO ASTHM T CS

RESULTS

The incidence of bronchial asthma about 2 00 of the population

The death rate from bronch asthma extremely low in recent ears abou per on of population

SUMMARY

The chief problem which occupies us here is the interaction of geographic climatic influences (sirocco khamsin sharav) some specific infections (Leishmaniasis) and the adaptation of the immense number of immigrants in the country The Jewish population of Israel had doubled within three years from 650 000 in mid 1948 to 1 300 000 in mid 1951 At the end of 1957 it has almost trebled and reached about two millions So far we know of only one special case of an epidemic of bronchial asthma due to adaptation difficulties

We differentiate our allergic cases of bronchial asthma as bacterial and non bacterial which may be or not be under the influence of psychic factors There are no particular allergic diseases characteristic of the country

For several years we have been working on statistics and found among a sample of 10 443 people in different parts of the country comprising 1690 families 139 asthmatics that is to say 1 3 p 100 of the whole population Most striking is the great incidence of asthmatic children

As causes we found fungi in 55 p 100 bacterial allergens in 41 p 100 pollen in 13 p 100 etc

Inside fungi in houses and bedding are more important than those in the air We prepare our extracts from the country s products and especially the patient s surroundings

It is important to know that we have here no ragweed and no rhus toxicodendron The hay fever season is reduced to the months March May

Skin tests diagnostic as well as treatment are mostly performed by the intracutaneous method

For a population of about 2 millions we have about 4 000 physicians (the proportion one physician 500 population) but more than 50 p 100 of these physicians are above 50 We have only 7 specialists in allergy and some part time allergists (one out of every 600 physicians is an aller gist in the United States one out of 40 physicians is an allergist)

We have an Israel Society of Allergy (since 1949) but no teaching facilities at the Hebrew University Medical School

The public is very allergy minded We find full cooperation even in primitive circles But there are limits owing to considerable economic *difficulties*

In recent years we have succeeded in reducing drastically the mortality rate from bronchial asthma which compared with that of other countries is low The total deaths from bronchial asthma has fallen from 45 in 1951 to 22 in 1956 Expressed as deaths per 100 000 population they have fallen from 3 2 in 1951 to 1 35 in 1956 We make this statement for the present without comment

RÉSUMÉ

Le probleme local primordial est celui de l influence géographico clima tique (Sirocco Khamsin Sharav) de certaines infections spécifiques (Leish maniose) et aussi celui de l adaptation du nombre considerable des immigrants

La population juive d Israel a doublé en trois ans de 650 000 au milieu de 1948 elle était de 1 300 000 a mi 1951 A la fin de 1957 elle se trouve avoir presque triplé et atteint environ deux millions d habitants

Nous ne connaissons qu un seul cas d épidémie d asthme bronchique imputable aux difficultés d adaptation des malades

Nous classons les cas d asthme allergique bronchique en asthme micro bien et en asthme non microbien des facteurs d ordre psychique pouvant intervenir pour ce dernier Il n y a pas en Israel de maladies allergiques particulieres au pays

Depuis plusieurs annees nous nous sommes livré a un travail de sta tistique sur 10 443 personnes habitant diverses parties du pays et repré sentant 1 690 familles 139 cas d asthme soit un pourcentage de 1 3 % pour l ensemble de la population La frequence de l asthme chez les enfants est a remarquer

Comme causes determinantes de la maladie nous avons trouvé les moisissures (fongi) pour 55 % des cas les allergènes bactériens pour 44 % les pollens pour 13 % etc

Les moisissures de l interieur des maisons et de la literie jouent un role plus important que les allergenes atmospheriques

Nous preparons nos extraits à partir des produits locaux plus parti culierement ceux prélevés dans l ambiance ou vit le malade

Il est important de noter qu il n y a en Israel ni Ambrosia ni Toxico dendron La saison du rhume des foins se limite a la periode de mars a mai

Les tests pour les diagnostics aussi bien que les traitements ont lieu en général par voie intradermique

On compte environ 4 000 médecins pour 2 millions d habitants (soit 1 médecin pour 500 habitants) mais la plupart d entre eux sont âgés de plus de cinquante ans Il n y a que 7 spécialistes de l allergie et un certain nombre d allergologues occasionnels (1 médecin sur 600 est allergologiste alors qu aux États Unis la proportion est de 1 pour 40)

Il existe en Israel une Société d Allergologie (depuis 1949) mais il n existe pas d enseignement spécial à l École de Médecine de l Université Hebraique

Le public est bien renseigné sur les questions allergiques nous trouvons une grande aide et une grande compréhension meme parmi les habitants les moins évolués Cependant les difficultes économiques viennent limiter nos possibilités

Depuis quelques années nous avons réussi à faire baisser dans une proportion considérable le taux de mortalité pour l asthme bronchique et ce taux est peu élevé si on le compare a celui d autres pays

Les morts dues a l asthme bronchique sont tombées a 22 en 1956 contre 45 en 1951 Pour 100 000 habitants cela représente un pourcentage de morts par l asthme de 1 35 en 1956 contre 3 2 en 1951 Pour le moment nous nous contentons d exposer ces faits sans commentaires

RESUMEN

El problema mas importante es el de la interrelación entre los factores geográficos y climáticos (sirocco khamsin sharav) algunas infecciones específicas (Leishmaniasis) y la adaptación del gran numero de inmigrantes que hay en Israel La poblacion judia de Israel se ha duplicado en tres anos pasando de 650 000 a mediados de 1948 hasta 1 300 000 a mediados de 1951 A fines de 1957 la cifra alcanzaba casi los 2 000 000 de habitantes Hasta el presente se conoce un solo caso de una epidemia de asma bronquial debida a dificultades de adaptación

El autor establece la diferenciación entre asma bronquial bacteriano y asma bronquial no bacteriano que pueden estar influidos o no por factores psíquicos No existen enfermedades alérgicas típicas del país

Una estadística realizada por el autor durante varios años y sobre un total de 10 443 personas de 1 690 familias dió una cifra de 139 asmáticos es decir el 1 3 p 100 de la población total Es notable la gran incidencia entre los niños

Los alergenos responsables son los *hongos* (55 *p* 100) alergenos bacterianos (41 p 100) y pólenes (13 p 100) Los hongos existentes en el interior de las casas y en los colchones son mas importantes que los que hay en el aire Los extractos utilizados se preparan a partir de materiales locales y en lo posible del mismo lugar del enfermo Es importante hacer notar que no hay ragweed ni Rhus toxicodendron en Israel La estación polínica se reduce a los meses de marzo abril y mayo Los *tests* se realizan en general por intradermo lo mismo que los tratamientos

Para una población de alr dedor de 2 millones de personas hay unos 4 000 médicos (1 cada 500 personas) pero el 50 p 100 de los mismos tiene más de 50 años de edad Hay solamente 7 especialistas de alergia y algunos

otros que se dedican a esa especialidad además de otra (En los E E U U la proporción de médicos alergistas es de 1 sobre 40)

Desde 1949 existe la Sociedad de Alergia de Israel No hay cursos especializados en la Universidad Hebrea

El publico tiene una muy aguda conciencia alergica y se encuentra una gran cooperación aun en los medios más modestos pero las posibilidades están limitadas por dificultades económicas

En los ultimos años se ha logrado reducir drásticamente la mortalidad por asma bronquial que es baja si se la compara con la registrada en otros países De 45 muertes en 1951 se ha reducido a 22 en 1956 Estas cifras referidas a 100 000 habitantes dan índices de 3 2 y 1 35 respectivamente Fl autor se limita a citar este hecho sin entrar a discutirlo

ZUSAMMENFASSUNG

Das hauptsachliche lokale Problem ist der geographisch klimatische Einfluss (Sirocco Khamsin Sharav) gewisse spezifische Infektionen (Leishmaniose) und die Adaptation einer betrachtlichen Zahl von Einwanderer

Die judische Bevolkerung Israels hat sich innerhalb von 3 Jahren verdoppelt von 650 000 im Jahre 1948 auf 1 300 000 im Jahre 1951 Ende 1957 hat sie sich beinahe verdreifacht sie hat ungefähr 2 Millionen Einwohner erreicht

Wir kennen nur einen einzigen Fall einer Asthma bronchiale Epidemie hervorgerufen du[illegible]

Wir teilen die [illegible]

Asthma und nic[illegible]

psychische Faktoren eine Rolle spielen. In Israel gibt es keine allergischen Krankheiten die spezifisch fur das Land waren

Seit einigen Jahren beschaftigen wir uns mit einer statistischen Arbeit uber 10 443 Personen die in den verschiedenen Teilen des Landes wohnen und einen Prozentsatz von 1 3 p 100 der Gesamtbevolkerung ausmachen Die Haufigkeit des Asthma bei Kindern ist bemerkenswert

Als auslosende Ursachen fur die Krankheit fanden wir Schimmelpilze in 55 p 100 der Falle bakterielle Allergene in 41 p 100 und Pollen in 13 p 100 der Falle usw

Die Schimmelpilze aus dem Hausinneren und des Bettzeuges spielen eine wichtigere Rolle als die atmospharischen Allergene

Wir stellen unsere Extrakte her indem wir als Grundlage ortliche Substanzen und solche nehmen die man in der Umgebung findet in der der Kranke lebt

Es ist wichtig festzustellen dass es in Israel weder Ambrosia noch Toxicodendron gibt Die Jahreszeit fur den Heuschnupfen ist auf die Monate Marz bis Mai beschrankt

Die diagnostischen Teste und auch die Behandlung werden im allgemeinen intradermal durchgefuhrt

Wir besitzen zirka 4000 Ärzte fur 2 Millionen Einwohner (1 Arzt auf 500 Einwohner) doch sind die meisten älter als 50 Jahre Es gibt nur 7 Spezialisten fur Allergie und eine gewisse Anzahl von gelegentlich Allergie

betreibenden Ärzten (1 Arzt unter 600 ist Allergologist während in den U S A das Verhaltnis 1 40 ist)

In Israel besteht eine Allergologiegesellschaft und eine Medizinschule der Hebraischen Universitat

Die Öffentlichkeit ist uber allergische Fragen gut unterrichtet wir finden grosse Hilfe und Unterstutzung auch bei den am wenigsten gebildeten Einwohnern. Hingegen grenzen okonomische Schwierigkeiten unsere Moglichkeiten ein

Seit einigen Jahren ist es uns gelungen die Mortalitatsquote fur Asthma bronchiale betrachtlich zu senken und diese Quote ist in Vergleich zu anderen Landern niedriger

Die Todesfalle haben sich von 45 im Jahre 1951 auf 22 im Jahre 1956 verringert Auf 100 000 Einwohner gibt das einen Prozentzatz von Todesfallen bei Asthma von 1 35 gegenuber 3 2 im Jahre 1951 Fur den Moment begnugen wir uns diesen Begebenheiten ohne weiteres Kommentar Beachtung zu schenken

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DEUTSCHLAND (*)

von

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EINLEITUNG

Ich werde nur einige wenige Fragen zu unserem Thema besprechen und zwar solche die von klinischem Interesse sind Uber experimentelle und theoretische Probleme werden kompetentere Forscher vortragen

Allergie ist ein pathogenetisches Prinzip und zwar eines unter vielen anderen es gilt nur fur einige Erkrankungen Wir kennen deren eine betrachtliche Anzahl aber sicher noch nicht alle

Krankheiten mit offensichtlich anderer Pathogenese (Trauma Abnutzung Vitaminmangel Infektion — Protozoen Bakterien Viren — Carcinogene Keimschadigungen etc) sollen nicht *sub specie allergiae* betrachtet werden doch muß ich einschrankend bemerken daß sich in dem Verlauf dieser Krankheiten allergische Vorgange einschieben und ihr Geprage mitbestimmen konnen Diese Varianten mochte ich aber nicht beruhren

KLINISCHES DILEMMA

Viele Erkrankungen die zu dem Kreis der allergischen gehoren werden abgesehen von den konventionell hierhin gerechneten (Heufieber Urticaria, Quinckeodem etc) nicht als solche erkannt weil aus traditionellen Motiven die Moglichkeit einer allergischen Pathogenese nicht erwogen oder a priori abgelehnt wird z B manche Krankheiten der Gefasse Bronchitiden Bronchiolitiden selbst Asthma bronchiale Emphysem und viele andere *Oder* aber manchen Erkrankungen wird vorzeitig eine allergische Pathogenese unterstellt obwohl entscheidende Beweise noch fehlen z B Polyarthritis rheumatica und Folgekrankheiten etc

PRAXIS ALLGEMEINE DIAGNOSTIK

Angesichts eines konkreten Krankheitsfalles wird der Kliniker moglichst unvoreingenommen zunachst die *Wahrscheinlichkeit* einer allergischen

(*) Pour des raisons indépendantes de nous ce rapport nous est parvenu incomplet nous nous en excusons auprès du lecteur

Pathogenese erwägen. Welche Indizien sprechen für Allergie: «allergische» Familien- und Eigenanamnese? Eosinophilie? Besondere Expositionsabhängigkeit von bekannten oder fakultativen Allergensubstanzen?

Erst dann sollte man mit Spezialuntersuchungen beginnen, um die Allergiehypothese zu verifizieren. Dies geschieht durch den Allergen- und Antikörper-Nachweis.

SPEZIELLE DIAGNOSTIK

1. genaue Anamnese, die wichtige Hinweise auf das spezifische Allergen gibt oder geben kann.

2. Ortsbesichtigung, die ebenfalls spezifischen Allergenhinweis bringen kann.

3. Hautreaktionen:

a) intracutan: Direktreaktion: Rötung und Quaddelbildung.

b) epicutan: Reaktion meist nach Stunden bis zu 48 Std.: Rötungen, Quaddel, Blasenbildung.

c) indirekte Cutanreaktion nach Übertragung des Antikörpers im Prausnitz-Küstner-schen Versuch. Auslösung durch intracutane Übertragung des Allergens in das Transplantationsfeld. — Varianten desselben: Auslösung durch *Inhalation* des Allergens (Aerosol), *peroral* durch Verfütterung des Allergens. — In beiden Fällen reagiert der Antikörper im Transplantationsfeld nach 10–60 Minuten. — Magensaftacidität beachten bei der peroralen Auslösung!

d) Expositionsproben durch:

α) dosierte Inhalation des Antigens. Messung der Schockfragmente (O_2-Sättigung des Blutes etc.) sowie im Pneumometrietest.

β) Verfütterung des Antigens transstomachal mit Duodenalsonde.

Die allgemeine Diagnose « Allergie » *(Pathogenese!)* genügt nicht, vielmehr ist der exakte Nachweis des *speziellen* pathogenen Allergens zu führen (« Ätiologie »), denn erst durch Nachweis der speziellen *causa peccans* ist der Weg zu einer kausalen Therapie frei.

THERAPIE

1. kausal: durch Karenz und Schutz vor neuen Allergen-invasionen je nach dem: inhalativen, nutritiven, contagiösen. — Besonders hervorzuheben: Medikamente als Allergene!

2. symptomatisch: durch Abschwächung der Symptome mit Hilfe von Pharmaca: Antihistaminica, vegetative Narcotica oder durch Verhinderung der allergischen Reaktion mit Cortison, Decortin etc.

Auf weitere spezielle Behandlungsfragen kann ich hier nicht eingehen.

Endogene Allergene durch Bakterienzerfall oder Gewebszerfall (Infektionskrankheiten! Focus!) sind bedeutungsvoll für Gefässerkrankungen, wahrscheinlich auch für die ganze Gruppe der rheumatischen Erkrankungen.

Klinische Erwagungen und therapeutische Beobachtungen sprechen fur die Allergennatur der genannten Erkrankungen ebenfalls patholo gisch anatomische feingewebliche Untersuchungen Ein exakter Aller gennachweis ist nur in sehr seltenen Fällen zu fuhren (z B morbus Bang u a)

Es ware sehr wichtig die betreffenden Allergene genauer herauszuar beiten um dann auch die oben genannten Proben mit ihnen durchfuhren zu konnen

Von besonders praktischer Wichtigkeit sind ausser den *genannten* exogenen Allergenen die Medikamente die z T als echte Antigene wirken (Insulin Leberpraparate Praparate endogener Drusen) z T als Haptene die sich erst nach Aufnahme in den Körper zu echten Vollantigenen complettieren — Die Haufigkeit der durch Medikamente ausgelosten allergischen Reak tionen ist Legion und praktisch viel bedeutungsvoller als etwa die durch nutritive Allergene aber auch diese sind besonders in der Kindheit von bedeutender Wichtigkeit (Kuhmilch Huhnerei Fisch u a)

Hohe Bedeutung haben die Inhalationsallergene fur den in industriellen und Werkstattbetrieben tatigen Arbeiter Es ware sehr erwunscht wenn die *Gewerbekrankheiten* noch weit mehr unter dem Gesichtspunkt der Allergie betrachtet wurden und nicht nur unter der Vorstellung dass die eingeatmeten Staubsorten rein physikalisch oder rein chemisch zu Erkran kungen der Atmungsorgane fuhren

Fur die *Hauterkrankungen* Kontaktdermatitis und Ekzeme ist die aller gische Entstehung mehr und mehr studiert auch als Berufskrankheit gegebenenfalls anerkannt worden auch hier mehren sich infolge der immer neu erfundenen Bearbeitungsstoffe die Anzahl der Erkrankungen

In Deutschland wird das Studium der allergischen Erkrankungen beson ders durch die Hautkliniken gefordert Fur die innere Medizin gibt es nur wenige Zentren und nur zwei Lehrstuhle bzw Lehrauftrage fur aller gische Erkrankungen in Berlin und in Kiel Eine Vermehrung dieser Lehrstuhle ist erwunscht — Die theoretischen Studien werden in allen serologischen Instituten betrieben teils mit teils aber auch ohne Verbin dung zu den Kliniken

JAPAN

by

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The so called allergic diseases are distinguishable from allergic diseases and allergy like diseases From the results of the investigations two factors are found to be required for the development of allergy first is the antibody diathesis and second is the neurolabile diathesis in the function of vegetatif system However we can sometimes recognize the manifestations quite identical with that of allergy which may occur without the former factor for example by administrating the foods containing the so called pseudo allergens (T Misawa) such as histamine neurine choline acetylcholine or by giving such substances subcutaneously or orally typical allergic syndrom can be produced in the individuals In these cases the syndroms are not produced by antigen antibody reaction in other words they are called to be allergy like Such allergy like manifestations seem to be connected with the state of unusual irritability of the autonomous nervous system especially of the parasympathetic nervous

From this point of view among the asthma there may be allergic and allergy like asthma, indeed the allergic asthma proved by the antigenicity is only 15 p 100 among the asthmatic patients Anyway asthma is one of the most important allergic diseases in Japan The frequency of it (0 3 0 45 p 100) is not so much different from the reports in other countries In general the asthma appears first at the age of 10 years or younger and the frequency of it is about one out of two or three The largest number of the allergic diseases in Japan is urticaria by investigating the medical history of urticaria at the mass medical examination it was found that about 30 p 100 of persons have anamnesis of urticaria The chronic type of urticaria is also comparatively frequent On the other hand we have to emphasize that hay fever is very rare in Japan though there are a few places around Tokyo where ragweeds grow gregoriously

CAUSES

INHALANTS As above mentioned hay fever is very rare in Japan and the main kinds of pollen in Japan seem to be pineaceae (pine cryptomeria) and gramineæ However the number of pollen allergy (conjunctivitis rhinitis vasomotorica) is not so great as the other allergic diseases This reason may depend upon the fact that it is rather rare that the same plants grow gregoriously in Japan Allergic diseases by house dust are comparatively few This may depend upon the difference of the constitution of the Japanese house and the mode of living of the Japanese from foreign countries Among asthmatic patients less than 10 p 100 were positive in skin test (scratch test) to house dust extract Allergic diseases by animal hairs and feathers are also seldom This is also concerned with the fact that most of the domestic animals are kept outdoors in Japan As the special and occupational inhalants in Japan Konnyaku asthma and Yokohama asthma were reported Konnyaku asthma was reported by Hichijo This type of asthma is only found in some small village in Gumma Prefecture where many factories of paste made from the starch of the devils tongue are gathered On the other hand Yokohama asthma was peculiarly found among the soldiers occupied in Japan The cause of it might be something like house dust or the soredium of soluble solvent

FOODS Foods are the most important factors of allergic asthma or urticaria in Japan Especially seafishes (mackerel bonito salmon salmon trout tunny etc) are most important because it is the main side dish of the Japanese and sometimes they are eaten raw Besides these lobster and crabs also become the cause of allergic diseases As for the vegetables spinach eggplant and bamboo shoot are important allergens A few cases of bean asthma were reported by Narise this is also rare, because it is the peculiar food of the Japanese

CONTACTANTS The most important and peculiar contactants for causing allergy in Japan are the lacquer gingko nut hair dye etc The number of allergic diseases by these contactants is comparatively high

INFECTIONS The frequency of the cases contracting asthmatic diathesis after infection is about 36 5 p 100 most of the infectious diseases are common cold bronchitis pneumonia whooping cough and *measles* and 16 5 p 100 of the cases get an asthmatic onset following a cold Th causative microorganisms of the infection are Streptococcus Neisseria Hæmophilus, Pneumococcus Staphylococcus etc

DIAGNOSIS

SKIN TESTS Scratch and intracutaneous tests as diagnosis means are not being commonly used The intracutaneous skin test has been mainly used but recently the scratch test is rather favourably used Its technique is similar to that of America or Europe Generally speaking the scratch tests are first tried and then intracutaneous injections are

performed only in the cases where reactions are positive or doubtful The concentration of the extract as antigen are varisies however usually 15 000-1 100 000 diluted solutions are used (calculate in N) The preparation of the extract is also variable depending upon the physicians As the type of reactions we give an important meaning to the acute type of reactions but we never neglect the meaning of delayed type of reactions However the delayed type of reactions tend to overlook clinically in the diagnosis of allergic diseases

TRIAL DIETS Misawa and Ogata s food test has been tried

TESTS WITH BACTERIAL EXTRACTS OR VACCINES It is only tried in some hospitals or Universities with cooperation of bacteriologists

THERAPY

DESENSITIZATION Specific desensitization is performed in the diseases in which its allergen is clarified but when the allergen cannot be determined non specific desensitizing therapy is performed

PROFESSIONAL AND EDUCATION

The number of physicians specialized in allergy is very small and the number of specialized allergy clinics in Japan is only two as follows

1 Doai Kinen Hospital (Tokyo) Number of physicians specializing in allergy (full time doctors 3)

2 National Sagamihara hospital (Kanagawa Prefecture) Number of physicians specializing in allergy (full time doctor 1)

Other part time physicians specializing in allergy may be over 200 On the other hand the total number of physicians may be 10 000 and they all deal with the allergic patients and pay a great attention to allergy Moreover the number of fundamental researchers of allergy in various fields of medicine is comparatively high

The Japanese Society of Allergy was established in 1952 and the number of the members is now over 1 000 Since then the General Meetings have been held annually and the organic magazines Japanese Journal of Allergy (reviews originals and English abstracts etc) have been published bi monthly However we have not a national allergic society as yet

Teaching on allergy has been done through the lectures of microbiology immunology pathology internal medicine dermatology and most of the other clinical lectures Therefore the lecture hours of allergy for medical students may be said to be about one hour per week Moreover allergy traching umwas imposed to the post graduate course of the university medical schools recently

PUBLIC ATTITUDE TOWARD ALLERGY The recent advancement of the antibacterial substance in the fields of medicine has rendered great services to the Society The progress in this field and the extension have caused the unexpected shock death (such as penicillin shock) in many cases However these facts have in creased to a great extent among the scientists and the population the interest in allergy and anaphylaxis

RÉSUMÉ

Voici les divers renseignements concernant les maladies allergiques et les problèmes sociaux et économiques que posent ces affections au Japon

Différentes maladies allergiques

Asthme Les cas d asthme ou de maladies reunies sous le nom d asthme sont relativement nombreux mais l asthme allergique ne represente que 15 p 100 de ce nombre

Urticaire le type aigu est frequent mais il existe egalement des formes chroniques qui ne sont pas rares

Rhume des foins on doit remarquer que cette affection est tres rare au Japon bien qu il y ait un assez grand nombre de régions ou les plantes du genre Jacobée sont abondantes

Causes des maladies allergiques

Pneumallergènes il y a peu de cas de manifestations allergiques dues à l inhalation de pollens De meme les manifestations allergiques respiratoires provoquées par la poussière de maison les poils d animaux et les plumes sont rares Ceci est du probablement à la différence dans le mode de construction des maisons et dans les mœurs des Japonais Une substance particuliere au Japon est constituee par une pate d amidon extraite d une plante appelée « langue du diable » qui est responsable de l asthme connu sous le nom de Konnyakuasthme

Produits alimentaires les aliments sont les facteurs les plus importants responsables de l asthme et de l urticaire allergiques Le poisson de mer est frequemment impliqué (maquereau bonito saumon truite saumonée) ainsi que le homard et le crabe Parmi les légumes citons les épinards et les tiges de bambou

Matières de contact les laques noix de gingko teintures capillaires etc

Médicaments penicilline aspirine antipirine sulfamides phénobarbital, etc

Diagnostic

Le diagnostic est pratiqué par l application de tests cutanés sous forme de cuti ou d intradermo reactions Dans les cas d allergie alimentaire on applique la technique de Misawa et Ogata

Thérapeutique

Dans tous les cas ou le diagnostic de sensibilisation a pu etre posé et ou la chose est possible on pratique la désensibilisation spécifique mais si la cause de l allergie n a pas pu etre determinee un traitement de désensibilisation non specifique est institué

Formation professionnelle et éducation

Il n existe que deux services hospitaliers spécialisés au Japon dans les maladies allergiques Actuellement tres peu de medecins s orientent vers cette specialisation Toutefois nombreux sont les médecins qui poursuivent des travaux de recherches sur l allergie dans les laboratoires de micro

biologie de pathologie et dans les services de médecine interne de dermatologie etc En général les cours sur ce sujet occupent environ une heure par semaine Cependant tout récemment un cours sur l allergie est devenu obligatoire pour les études post universitaires de l Academie de Medecine

Attitude du public en face des problèmes allergiques

Les progres récents et remarquables dans le domaine des antibiotiques ont rendu de grands services à l humanité mais d autre part l extension de l emploi des antibiotiques a cause une augmentation importante des accidents allergiques et meme des cas de mort soudaine par choc anaphylactique à la suite d injection de pénicilline Ces accidents ont contribue a éveiller un intéret croissant parmi les hommes de science et aussi dans le public pour les problemes d allergie

ZUSAMMENFASSUNG

Allergische Erkrankungen in Japan

Asthma es gibt verhaeltnismaessig viele Faelle von sogenanntem Asthma aber nur 15 p 100 davon beruhen auf Allergien

Urticaria akute und chronische Faelle sind verhaeltnismaessig haeufig

Heuschnupfen Heuschnupfen ist in Japan relativ selten obwohl an einigen Orten in der Umgebung von Tokio Jakobs Kreuzkraut reichlich waechst

Aetiologie

Inhalations allergene Pollenallergie kommt selten vor ebenso durch haeuslichen Staub und Federn hervorgerufene Allergien Dies duerfte auf die andersartige Bauweise der japanischen Haeuser und auf die verschiedene Lebensweise der Japaner zurueckzufuehren sein « Konnyaku Asthma wird als » besondere durch Einatmung bedingte Berufserkrankung hervorgehoben Verantwortlich dafuer ist der Staerketeig aus der sogenannten « Teufelszunge »

Nahrungs und Genussmittel sie sind die haeufigsten Ursachen von allergischen Asthma und Urticaria Erwaehnenswert sind besonders Salzwasserfische (Makrelen Tunfische Lachs Lachsforellen) Manchmal koennen auch Hummern und Krabben als Allergene wirksam sein Weiters sind Spinat Eierpflanzen und Bambusschotten haeufig anzutreffende Allergene

Kontakt Allergene Lack Gingko Nuesse Harrfaerbemittel usw

Medikamente Penicillin Pas Aspirin Antipyrin Sulphonamide Luminal usw

Diagnostik

Kutanteste Kuti und Intradermalteste

Teste auf Nahrungsmittel Untersuchungen nach Misawa und Ogata

Therapie

Wenn sichere Allergene festgestellt werden konnten dann spezifische Desensibilisierung Wenn das Allergen nicht nachzuweisen ist dann unspezifische Desensibilisierung

Studium und berufliche Ausbildung

Derzeit existieren nur 2 Spezialkliniken fuer Allergie auch die Zahll der Allergie Spezialisten ist sehr gering Hingegen befassen sich ziemlich viele Forscher mit allergischen Problemen der verschiedenen medizinischen Spezialgebiete Zum Beispiel wird in der Woche eine einstuendige Vorle sung ueber Allergie in der Mikrobiologie Immunologie Pathologie Inneren Medizin Dermatologie und in anderen medizinischen Spezialgebieten durchgefuehrt Kuerzlich wurde den Fortbildungskursen der Universi taetsklinik eine Allergie Abteilung angegliedert

Einstellung der Bevoelkerung zur Allergie

Die bemerkenswerten Fortschritte der Antibiotika Therapie haben der Bevoelkerung auf dem Gebiete der Medizin grosse Dienste geleistet Anderenseits sind auch Todesfaelle durch Schock aufgetreten (z B Penicillinschock) Dennoch haben diese Tatsachen das Interesse und die wissenschaftliche Erfahrung aud dem Gebiet der Allergie bedeustend vertieft

RESUMEN

Enfermedades alérgicas en el Japon

Asma existe una gran cantidad de tipos de asma pero los casos en que el alergeno ha podido ser encontrado constituyen solamente el 15 p 100 del total

Urticaria tanto el tipo agudo como el crónico son relativamente abun dantes

Fiebre de heno es muy rara en el Japón aunque debe hacerse notar que hay ciertos lugares alrededor de Tokio donde crecen en abundancia especies del genero Ambrosia

Causas

Inhalantes el numero de casos debidos al polen es pequeno El polvo doméstico los pelos de animales y las plumas son de poca importancia probablemente como consecuencia del tipo de construcción de las casas japonesas y del modo de vivir de sus habitantes En cuanto a los inhalantes especiales que se aspiran en algunas profesiones se ha señalado la exis tencia del asma llamada «Konnyaku» producida por una pasta del almidón de una planta llamada lengua del diablo

Alimentos constituyen el factor más importante en la aparición de asma y urticaria Son importantes los pescados (caballa bonito salmón trucha etc) langostas y cangrejos Entre las verduras son importantes las espinacas berenjenas y brotes de bambu

Alergia de contacto laca nuez «Gingko» tinturas para cabello, etc

Drogas penicilina pas aspirina antipirina, sulfamidas luminal

Diagnostico

Tests cutáneos a veces se efectuan cuti e intradermorreacciones

Tests con alimentos se efectuan con alimentos de Misawa y Ogata

Tratamiento

Se lleva a cabo la desensibilización específica cuando se ha podido identificar al alergeno en los demás casos se practica un tratamiento no específico

Especialidad y educacion médicas

Hay actualmente sólo dos clínicas especializadas en alergia en el Japon y el numero de médicos especialistas es también muy limitado Sin embargo el numero de investigadores en los diferentes campos vinculados a la alergia es relativamente grande Se dan clases sobre alergia en las cátedras de microbiología inmunología patología medicina interna dermatologia etc. pudiendo decirse que hay alrededor de una hora semanal de conferencias sobre alergia en cada universidad Ultimamente se ha establecido un curso obligatorio sobre alergia en el departamento de post graduados de la Universidad

Reacción publica ante la alergia

El progreso notable aportado por el uso de los antibióticos ha traído por otra parte una serie de accidentes (como el *shock* producido en ciertos pacientes por la penicilina) Sin embargo estos hechos han despertado un gran interés en el estudio de las enfermedades alérgicas y han contribuido de esa manera al progreso científico

URUGUAY

por

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Plantear el problema especial de las *proyecciones sociales* de la alergia equivale a plantear el problema específico de las proyecciones sociales de los estudios alérgicos y lo que es *más* importante plantear el problema general de *proyecciones sociales de la Medicina*

Hace ya tiempo se ha hecho conciencia acabada acerca de la convicción de que la Medicina ha dejado de constituir una *profesión particular* para constituir una función social ejercitada por particulares

En los países donde se ha ido derechamente a la socialización de la medicina o estatización de la medicina la salud de los ciudadanos ha dejado de constituir una preocupación privada para erigirse en preocupación pública y radicar en ella por consiguiente el denominador común de la Salud Pública *como se dice en nuestro país*

Adviertase que no se trata solamente de que el Estado se [illegible] salud de los ciudadanos [illegible] alotrópica de la misma [illegible] constituya un servicio [illegible] algo más se trata de que aquella [illegible] de la ciencia y aquel arte *especial* que integra lo que entendemos por medicina constituya una actividad ineludible de la sociedad constituida en Estado y por encima de los Estados se integre en la sociedad internacional

No reputo lejano el día en que del mismo modo en que actualmente en las fichas individuales se incluyen entre otros datos sobre lugar de nacimiento fecha origen etc, se inserten asimismo *como los grupos sanguíneos los test* la alergia medicamentosa etc

Sabemos que dependen de circunstancias orgánicas y de circunstancias ambientales los filósofos hablan del yo y del contorno del yo del ser y de las circunstancias del hombre y del medio

Los filósofos no hablan así por mero pretexto *ni por mero lujo* verbal Lo hacen *porque* en pocas palabras de sentido aparentemente oscuro dicen una profunda verdad *válida* no sólo para los ámbitos del pensamiento metafísico sino para los ámbitos de esta actividad nuestra de este quehacer nuestro que no está más allá de la *física* como quiere decir la palabra *meta física* sino que está más acá en lo profundo del ser humano en

su dolor en su angustia en su sed de supervivencia espiritual y material

Yo y mis circunstancias tal podría ser el lema del hombre nuestro en la medicina social, en la medicina considerada como una dependencia de la Sociologia como un sacerdocio que mira la cura de cuerpos del mismo modo como el otro estima la ' cura de almas

Y en cierta medida ¿no aparejamos nosotros los medicos los instrumentos necesarios para que el cuerpo asiento del alma viva mejor y cultive mejor la pureza de espíritu? ¿No propendemos de esa manera a formas superiores de vida en donde se consustancian el espíritu con la materia en donde la superación del dolor equivale a la superación de la vida?

Escribía el profesor Emilio Mira y Lopez en 1944 cuando se preveía el fin de la guerra venturosamente favorable a las democracias occidentales de que formamos parte en un libro (El munto de post guerra) destinado a encarar los problemas emergidos de la cesación victoriosa de las hostilidades El progreso técnico o material de nada sirve si no se acompaña de un mejoramiento ético social de los pueblos que lo exhiben Es evidente que en lo sucesivo se atenderá mas al criterio científico para elevar la actitud ético social del hombre medio así como para asentar las bases que regulen las relaciones internacionales La sanción de los vicios es menos efectiva que su previsión Si la actual hecatombe mundial no ha de ser una muestra más de la infinita estupidez humana hay que esperar que sirva para crear nuevas reglas de convivencia comprensión y solidaridad lo que plantea la necesidad de escuchar la opinion de los psicohigienistas para la estructuración de los nuevos Estados

Adaptando esos razonamientos al actual estado de cosas de la humanidad hemos visto que no se han cumplido tan generosas previsiones Pero los principios enunciados se mantienen intactos no habrá mejoramiento de la humanidad sin mejoramiento ético social del individuo debe atenderse sin embargo el criterio científico para elevar la actitud etico social del hombre medio prever antes que sancionar y escuchar la opinión del hombre de ciencia para la estructuración de la sociedad nacional y de la sociedad internacional

No sólo de pan vive el hombre se ha dicho pero comienza por vivir de pan. Mejoremos las condiciones sociales, económicas de salud como forma previa al mejoramiento espiritual ningun objeto puede perseguirse con aquel mejoramiento si no tiende a este ultimo No descuidar los fines generosos y desinteresados de la ciencia

Prever más que sancionar prevenir antes que curar No creo que los nuevos Estados acusen el grado de adelanto que todos deseamos el bien de la libertad y de la independencia no parece haberles resultado propicio para el debido asentamiento de los mismos

Nuestra ciencia nuestra actividad nuestro quehacer el estudio de las enfermedades alérgicas ¿no tiende precisamente a todo eso? No procura hacer innecesario el remedio impidiendo la enfermedad? ¿Puede un hombre publico serlo enteramente sin que estudios como los nuestros y actividades como nuestras actividades obtengan no solamente la debida protección el debido respeto?

Debemos insertar nuestras preocupaciones profesionales pues en el inmenso campo de la sociologia politica y desde luego en el no menos inmenso campo de la política social inversión de terminos que no supone

mero juego de palabras Si para Valery ha existido una política del espíritu cómo no habría de existir una política del cuerpo ?

Hoy en nuestro país hay clínicas alérgicas en instituciones tales como el Ministerio de Salud Publica en lo que concierne a los factores que inciden sobre los accidentes de trabajo y especialmente en las llamadas enfermedades profesionales Todo en el hombre es una profesion todo en el hombre está sujeto a enfermedades de esa naturaleza toda actividad del hombre comenzando por la actividad primigenia y elemental de vivir de existir en el planeta está sujeto a nuestro quehacer científico y a nuestro quehacer histórico tanto que quiéralo que no Unamuno ha confesado que advierte cómo desde el momento mismo en que nacemos comenzamos ya a morir y que nuestra existencia no es mas que una serie de muertes sucesivas de enfermedades sucesivas de triunfos sobre la enfermedad.

Es ese triunfo el que la alergia procura asegurar como faena de este mundo en que vivimos para hacerlo mejor y para que de mas en mas se parezca al que nos espera más allá de la muerte

¿Puede acaso confiar en la existencia de una actividad mejor y más noble que la nuestra?

No es el caso de que se organicen y funcionen pues clínicas alérgicas o de alergistas Es menester que todos los organismos del Estado se hallen en todo instante prontos y dispuestos para proporcionarnos los materiales que hemos menester

Nuestras facultades deben orientar científicamente a los estudiantes en el sentido indicado nuestros laboratorios deben hallarse siempre dispuestos a realizar las investigaciones necesarias Y hasta no es aventurado pensar en que un día entre los días exista une especie de central de estudios y de investigaciones con tal acopio de datos que haga advertir que del mismo modo como fichamos a todos los individuos por sus huellas dactilares tengamos junto con la historia clínica de cada individuo un estudio de sus *test* alérgicos que hagan de la medicina lo que la medicina debe ser no la función del genio sino la rutina de una función permanente Luchar como se luchó contra la tuberculosis contra el cáncer contra la sífilis contra las enfermedades venéreas contra la poliomielitis contra las afecciones cardíacas Luchar en los grandes planos y en los grandes frentes ver el bosque no solamente los árboles ver el árbol no solamente sus hojas

Afirmo rotundamente que ese día no está lejos afirmo rotundamente que su necesidad es fácil de apreciar por todos Afirmo confiadamente en que las dificultades no son de orden técnico sino quizá de orden economico creo asimismo que los defectos de organización pueden superarse con relativa facilidad Sólo se necesita un poco de comprensión un poco por decirlo de simpatía en lo que la simpatía tiene de fe del hombre para con el hombre de confianza del hombre en el porvenir del hombre de esperanza en el porvenir

Para ajustarme a lo limitado d l tema he debido recurrir a esas consideraciones de orgen general que en forma alguna reputo ociosas Antes al contrario considero que en el Uruguay no todo está por hacer es mucho lo que se ha hecho si bien es cierto que en forma inorgánica y a impulso de ponderados esfuerzos individuales

Pero las mismas consideraciones que valen para todos los Estados valen

desde luego para el Uruguay En el Uruguay es el Ministerio de Salud Publica el que se encarga del estudio de los enfermos alérgicos en clinicas hospitalarias y con un Servicio Profesional de Alergia

Podemos afirmar sin temor a dudas de que tanto en el cuerpo médico en general como en el publico hay formada ya una verdadera conciencia alérgica Incluso en el lenguaje comun la palabra alergia ha adquirido ya, de hace mucho tiempo carta de ciudadanía Quizá eso constituya un inconveniente nada es más peligroso para la ciencia que la deformación popular de los conceptos científicos Einstein tuvo que luchar duramente para que no confundiesen su relatividad con el relativismo filosófico o científico la gente acudía a sus conferencias por moda por curiosidad por snobismo y salía desilusionada porque no entendía Como si el entender fuera una condición *sine qua non* de validez de las verdades científicas

Entre nosotros es comun decir le tengo alergia ' a una persona a una cosa a un tema a una idea como sinónimo de prevencion cautela repulsión y no pocas veces odio o aversión

Será menester efectuar una intensa campaña educativa como forma unica de defender al pueblo del charlatanismo y del engaño de las falsas obsesiones y de las falsas seguridades nada podremos decir de la alergia que no digamos y hayamos de decir por idénticas razones de la medicina en general

He procurado extenderme en referencias que salgan de los limites que podrían resultar de una mera «comunicación» y hacer de este breve estudio una toma de contacto con realidades que a todos interesen y que todos por igual con iguales o mejores razones que yo, pueden advertir

RESUMEN

El tema elegido para tratarlo en un simposio del III Congreso Internacional de Alergia es de mucho interés porque es la alergia una de las especialidades que más vinculacion tiene con la medicina preventiva y por lo tanto es importante la acción social del médico en esa especialidad llevando al pueblo el problema de la alergia dando las directivas necesarias para tratar de prevenirla

Hace tiempo que se ha hecho conciencia que la medicina ha dejado de constituir una profesion particular y se va llegando a su socialización Llegará el día en que en las fichas individuales se incluyan con los datos de nacionalidad fecha de nacimiento, estado etc datos médicos como vacunas analisis resultado de la testificación alérgica intolerancias medicamentosas etc

«Yo y mis circunstancias» podria ser el lema del hombre nuestro en la medicina social

Dijo Mira y Lopez en 1944 «El progreso técnico material de nada sirve si no nova acompanado de un mejoramiento social de los pueblos» No habrá mejoramiento de la humanidad sin mejoramiento ético social del individuo prever antes que sancionar

Se debe mejorar las condiciones sociales económicas de salud como forma previa al mejoramiento espiritual

La Alergia no sólo trata la enfermedad alérgica en sí sino la repercusión

de la misma en las profesiones la llamada alergia profesional la que más tiene repercusión en lo social y donde se puede hacer una efectiva profilaxis que favorece al obrero a la industria y al patrimonio nacional aumentando la producción haciendo además al obrero más feliz dándole salud bienestar y seguridad en su trabajo

En nuestro país el Uruguay ya hay *conciencia de la alergia* tanto en el cuerpo médico como en el pueblo Ya la palabra alergia ha adquirido su *carta de ciudadanía*

RÉSUMÉ

Le theme choisi pour etre traité dans ce symposium du III^e Congres International d Allergologie presente un tres haut intéret L allergologie est une des spécialités les plus étroitement liées à la médecine preventive et de ce fait, l œuvre a accomplir par le médecin allergologiste est considérable Il doit faire connaitre au public les problemes posés par l allergologie et donner les directives nécessaires pour s efforcer de la prevenir

On a pris conscience depuis longtemps dejà du fait que la profession médicale a cesse d etre une activité privée et elle tend à prendre le caractere d une fonction sociale Un jour viendra ou les fiches personnelles mentionne ront en plus de la nationalité de l interessé sa date de nai sance sa situation de famille etc des renseignements médicaux concernant ses vaccination ses analyses les résultats des tests allergiques son intolerance particuliere aux médicaments etc

« Moi et mes particularités » telle pourrait etre la devise de l homme du point de vue de la médecine sociale

Mira y Lopez a dit en 1944 « Le progrés technique est inutile s il n est pas accompagné d une amelioration sociale des peuples » Il ne saurait y avoir une amélioration de l humanité sans amélioration ethico sociale de l individu mieux vaut prevoyance que sanction

On ne peut parvenir a l amélioration spirituelle que par l amélioration préalable des conditions sociales economiques et de la santé publique

Les problemes de l allergie ne se limitent pas à etre ceux des maladies allergiques considerees uniquement comme telles mais comportent aussi leurs repercussions dans le domaine professionnel ce que l on nomme « allergie professionnelle » est une des maladies dont les repercussions sociales se font le plus sentir et contre laquelle il faut pour le bien de l ouvrier prendre des mesures de prophylaxie efficaces Elles ameneront une amelio ration certaine des conditions du travail industriel et seront profitables au patrimoine national et à l augmentation de la production. L ouvrier connaitra une vie plus heureuse plus de bien etre et plus de sécurité dans son travail

Dans notre pays l Uruguay aussi bien le Corps Medical que le public ont pris conscience des problemes de l allergie D ores et dejà le mot allergie a acquis ici son droit de cité

SUMMARY

The theme chosen for the discussion is of a great interest Allergology is one of the medical specializations the most closely linked to preventive

medicine and therefore the physician s social task is an important one His duties are to keep the public informed on allergic problems and to give the necessary advice for the prevention of allergic diseases

For some time already, we have become aware of the fact that the medical profession has ceased to be a private one and is on the way of growing into a social and public duty

The day will come when individual files shall bear besides indications such as nationality date of birth and so on medical information on vacci nations analysis result of allergological tests particular intolerance to drugs etc

Me and my particulars might become the motto of men considered from the point of view of social medicine

In 1944 Miro y Lopez said Technical progress is useless unless it is accompanied by the social improvement of the people There can be no improvement of humanity without an improvement of the individual foresight should be preferred to sanctions

Before one can expect spiritual improvement better social economical and health conditions must have been achieved

Allergy does not only consist in the allergic diseases but also in its conse quence for occupational life so called occupational allergy is one of the pathological disturbances having strong incidence in social life and for which for the sake of the working class efficient prophylactic measures should be enforced Such a policy would bring about an improvement of industrial economical conditions and of the national patrimony an increase of production and would thus give the workers happier living conditions more comfort a better health and more security in their work

In our country the Uruguay the physicians as well as the public are well aware of the allergic problems The word allergy has won in this country its rights of citizenship

ZUSAMMENFASSUNG

Das fur dieses Symposium des III Internationalen Allergologie Kongresses gewahlte Thema ist sehr interessant Die Allergologie ist eine der am engsten mit der praventiven Medizin verbundenen Spezialitaten und deshalb ist das vom Allergie Facharzt zu bewaltigende Werk betrachtlich Er soll die Öffentlichkeit mit den Problemen der Allergologie vertraut machen und die zu Praventivmassnahmen notwendigen Anweisungen erteilen

Man stellte schon seit langerer Zeit fest dass der arztlicher Beruf auf gehort hat nur eine private Betatigung zu sein und er neigt immer mehr dazu den Charakter einer sozialen Funktion anzunehmen Es wird der Tag kommen da werden die Personaldokumente nicht nur die Daten uber Nationalitat Geburtsdatum Daten uber Familienverhaltnisse etc aufwei sen sondern auch arztliche Auskunfte uber Vaccinationen Analysen Ergebnisse von Allergietests besondere Medikamentenintoleranz etc enthalten

Ich und meine Eigenheiten konnte vom Standpunkt der Sozialmedizin aus das Moto fur den Menschen sein

Mira y Lopez sagte 1944 Der technische Fortschritt ist unutz wenn er

nicht mit einer sozialen Verbesserung des Volkes einhergeht Es wird keine Besserung der Menschheit eintreten wenn nicht eine Besserung des Einzelindividuums in etisch sozialer Hinsicht erfolgt Voraussicht ist besser als Bestrafung

Man kann nur zu einer geistigen Besserung gelangen, wenn man vorher die sozialen okonomischen Verhaltnisse und die Volksgesundheit bessert.

Die Probleme der Allergie beschranken sich nicht nur auf die allergischen Erkrankungen als solche sondern haben auch ihre Ruckwirkungen auf das Berufsleben, was man Berufsallergie nennt und was eine der Krankheiten ist deren soziale Ruckwirkungen viel zu denken geben und gegen die man zum Schutze des Arbeiters mit aller nur wirksamen Prophylaxie ankampfen muss Sie werden eine gewisse Besserung der Arbeitsbedingungen bewirken und so nutzbringend fur das Nationalvermogen und eine Produktionserhohung sein. Der Arbeiter wird ein glucklicheres Leben kennen lernen wird sich wohler fuhlen und einen sicheren Arbeitsplatz haben

In unserem Lande Uruguay nimmt sowohl die Ärzteschaft als auch die Öffentlichkeit lebhaften Anteil an den Allergie Problemen Das Wort Allergie hat hier bereits sein Burgerrecht erworben

SOME PECULIARITIES OF THE ALLERGENIC FLORA OF BRAZIL

by

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I selected to present at this Symposium some of the peculiarities pertinent to the Brazilian flora and which may be of some interest to allergists from other parts of the world

A PECULIAR CLASS OF ALLERGENS

A very curious peculiarity existing in Brazil is that in relation to the variety of substances commonly used for the stuffing of pillows cushions chairs sofas mattresses etc and which may act as inhalant allergens Though cotton linter kapok wool feathers and horse hair are the most common substances employed here for stuffing many others are also used by the poor class of our population These substances are distributed among different families of plants and are represented by their flowers seeds or leaves The following families are the most important *Gramineæ* the flowers or the pilous seeds from *Erianthus asper* *Andropogon saccharoides* *Tricholæna rosea* *Saccharum officinale* the leaves of *Zea mays* *Typhaceæ* the flowers from *Typha dominguensis* Very often a great amount of pollens is found in pillows and mattresses made with these flowers *Trigoniaceæ* the pilous seeds from the genus *Trigonia* *Compositæ* the flowers from *Achyrocline satureoides* and *Stenocline Gardneri* *Convolvulaceæ* the pilous seeds of the genera *Ipomea* and *Bonamia* *Bromelliaceæ* the seeds covered with silky hairs from the genera *Vriesea* *Catopsis* *Tillansia* *Apocynaceæ* the seeeds in general with a brush of fine hairs at the extremities from almost any genera of the sub family *Echitnideæ* (*Mesechites* *Mandevilla* *Prosterona* *Secondatia* *Odontadenia* *Galactophora* *Peltastes* *Stipecona* *Prestonia* etc) *Asclepiadaceæ* the seeds crowned with a bundle of hairs from the genera *Asclepias* *Araujia* *Blephorodon* *Shubertia* *Hoya* *Ibatia* *Marsdenia* *Metastelma* *Cryptostegia*

Colotropsis Gomphocarpus Exolobus etc *Bombaceæ* the seeds and their fibers from the genera *Bombax Chrosisia Eriodendron Ochroma Ceiba Adamsonia Matisia* In Brazil there are more than 30 species of the *Bombaceæ* family all producers of *kapok*

THE CULTIVATED GRASSES OF BRAZIL

The *Gramineæ* of greater interest in endemic pollinosis in almost all countries are among the species cultivated for pasture specially because they produce larger amount of pollens than the native species

The principal species of grass cultivated in Brazil to secure forage are the following *Hyparrhenia rufa Melinis minutiflora Panicum maximum Panicum purpurascens Paspalum notatum Paspalum dilatatum Paspalum conjugatum Paspalum maritimum, Paspalum fasciculatum Cynodon dactylon Chloris goyana Axonopus scoparius Pennisetum purpureum Tricholæna rosea Bracchiaria plantaginea Echinochloa polystachya Heteropogon villosa Digitaria saguinalis Bromus catharcticus Shorgum sudanensis*

Among the species of primary or secondary importance in endemic pollinosis in other countries (*Phleum pratense, Poa pratensis Cynodon dactylon Dactylis glomerata Agrostis alba Bromus inermis Holsus lanatus Anthoxanthum odoratum Paspalum dilatatum Lollium perenne Lollium multiflorum*) only *Cynodon dactylon* is widely distributed here This species presents in Brazil the same peculiarities (perennial pollinization etc) exhibited in other countries The species *Poa pratensis Phleum pratense Dactylis glomerata Holcus lanatus Lollium perenne Lollium multiflorum* only recently are being cultivated in the Southern States of Brazil The acreage covered at present by these species are negligible

According to our studies carried out since 1942 *Melinis minutiflora* on account of its great output of pollens per individual plant and its large acreage is the only species of grass that fulfills for a large area of the Brazilian territory the necessary conditions for a plant to be of primary importance in endemic pollinosis

THE BRAZILIAN *COMPOSITÆ*

In addition to members of the *Compositæ* family considered of secondary importance in other coutries *(Solidago, Aster Xanthium Parthenium Helianthus Erigenron)* many other genera are widely distributed throughout the Northern, Central and Southern States of Brazil (*Achyrocline Baccharis Calea Eupatorium Mikania Bidens Eremanthus Senecio Vigniera Wedelia Vernonia* etc) However most of the wild and cultivated species of the genera produce only a small amount of large pollen grains better adapted to insect transport

The members of the *Compositæ* family of primary importance in pollinosis in North America *(Ambrosia Iva Franseria Artemisia)* are not abundantly distributed in Brazil *Ambrosia polystachya A artemisiaefolia* and *A tenuifolia*, our principal species of the family can be seen as inhabitant of vacant lots roadsides and waste areas in many of our towns

However none of these species have an acreage great enough to be an important hay fever factor at present in Brazil

In some areas a very small and inconstant amount of pollens grains with short spines is caught on our slides Identification of such pollen has not yet been possible but there is some suspicion that a major part of it comes from members of *Parthenium Taraxacum* or *Baccharis*

THE *CHENOPODIALES* IN BRAZIL

Members of the families *Amaranthaceæ (Amaranthus Acnida Chamissoa Pfaffia Iresine Gomphrena Celosia)* and *Chenopodiaceæ (Chenopodium Atriplex Kochia Salsola Spinachia Beta)* are widely distributed throughout all States of Brazil However in spite of the apparently abundant distribution of certain species *(Amaranthus hybridus A viridis A retroflexus A spinosus Chenopodium ambrosioides Ch hircinum Atriplex montevideensis* etc) which can be seen as inhabitant of fields gardens and vacant lots in our town their acreage is still too small as proved by the negligible number of pollens grains of the *Amaranthus Chenopodium* type caught on our slides

THE ONLY POLLEN SEASON OF BRAZIL

Our interest on pollinosis in Brazil dates from 1939 and in 1942 we began publishing regularly the results obtained from our studies regarding the incidence of pollens in the atmosphere of our towns According to the studies only one definite pollen season was found to exist in Brazil This season has occurred each year from the middle of May to the middle of June only in regions (Central and Southern States) were *Melinis minutiflora* was the principal grass cultivated for pasture We never found such a pollen season in regions where other species of grass are used to secure forage

Although several members of the grass family are now being cultivated in Brazil only a few species have their pollinating period in the middle of the year Among them are *Melinis minutiflora Panicum maximum Hyparrhenia rufa Cynodon dactylon Panicum purpurascens* Since atmospheric studies are not helpful in evaluating the grass pollens caught on * we had some difficulties in the determ[illegible] sible for our season from May to Ju[illegible] because it generally reaches anthesis [illegible] *Melinis minutiflora Hyparrhenia ru*[illegible] *[illegible]um purpurascens* were found blooming in areas where pollen seasons was never found *Cynodon dactylon* as in other tropical and semitropical countries have no definite pollinating period and blooms almost perennially when weather conditions are favorable Besides its output of pollen appear to be small

By a close check of pollinating habits of our most common forage grasses and the amount of pollen in the air we could show that *Melinis multiflora* is the principal species responsible for the only pollen season we have in Brazil

HAY FEVER A RARITY IN BRAZIL

Although the incidence of allergic diseases is apparently similar to that registered in other countries hay fever is considered a rarity in Brazil It is interesting to note that although we have a very definite pollen season the grass season which occurs regularly from the middle of May to the middle of June in a large area of our territory only three typical cases of hay fever have as yet been reported in Brazil Curiously all these three cases were of patients descending from foreign parents no cases of hay fever have been reported among native Brazilians

Various hypothesis were formulated in the past to explain the rarity of hay fever in Brazil 1º lack of susceptibility of Brazilians to pollen antigens 2º low density of pollen grains in our atmosphere 3º short duration of our pollen season 4º the possibility that cases of hay fever are passing unperceived to our allergists

ABOUT THE FAMILY *ANACARDIACEÆ*

The family *Anacardiaceæ* with more than 60 genera and 700 species are plants of worldwide distribution chiefly trees with some shrubs and vines Several species are widely cultivated in various tropical countries for their edible fruits including representatives of *Spondias Dracontomelon Pleiogynium Odina Pistacia Cystocarpa Lannea Harphyllum Mangifera Semecarpus Anacardium Gluta*

In general this family has a more or less resinous or milky sap which soon turns brown or black on exposure to the air The sap of some species of *Rhus Gluta Lithraea Schinus Melanorrhoea* is the basis of certain types of lacquer Only a few species of some genera such as *Rhus Toxicodendron Lithraea Anacardium Semecarpus Gluta Mangifera* that are actually poisonous acting their sap as a primary irritant It is this sap that carries the allergenic principle (a catechol derivative) which on contact with the skin causes the characteristic dermatitis on a susceptible person Not all genera possess this catechol derivative as the allergenic factor

Among the different genera of *Anacardiaceæ* some are confined to certain parts of the world The genus *Rhus* and the segregate genus *Toxicodendron* are confined to North America Japan and China The genera *Gluta Swintonia Melanorrhoea Melanochyla Semecarpus Campnosperma Mangifera* (the poisonous species) are all characteristic of the indo Malayian region The genera *Anacardium Mangifera Spondias Pistacia Schinus Schinopsis Lithraea Astronium, Metopium Pseudosmodigium* are characteristic of South America

THE BRAZILIAN MEMBERS OF ANACARDIACEAE

Among the 40 representatives of *Anacardiaceae* found in Brazil the following are the most important species *Anacardium occidentale A giganteum A nanum A humile Astronium concinnum A commune A fraxinifolium A urundeuva Lithraea molleoides L brasiliensis L caustica Mangifera indica Pistacia lentiscus Schinus mole Sch lentiscifolius Sch terebinthifolius Sch spinescens Sch dependens Sch Weinmanniaefolius Schinopsis Lorentzii Sch balansae Sch brasiliensis Spondias purpurea Sp lutea Sp dulcis Sp mangifera Sp tuberosa*

TOXICODENDRON VERSUS *LITHRAEA*

Although several of *Anacardiaceae* have a potent skin sensitizing factor the genera *Toxicodendron* in North America and *Lithraea* in South America are the most widely distributed and the most important for the allergist

The allergenic principle of the genus *Toxicondendron* is said to be a catechol with an unsaturated side chain and the chemical function of a polyhydric phenol All species of this genus (*Toxicodendron radicans T quercifolium T diversiloba*) seem to contain identical antigens Patients sensitive to one species react quantitatively to the allergenic factor of the other species

We have shown that the antigen of the genus *Toxicodendron* is also found in the three species of the genus *Lithraea* Guinea pigs sensitized to the oleoresin from *Lithraea molleoides* cross reacted to oleoresins from *Lithraea brasiliensis Lithraea caustica Toxicodendron radicans T quercifolium* and *T diversiloba* Similar results showing this cross reaction between the genera *Toxicodendron* and *Lithraea* were also obtained in experiments carried out in patients hypersensitized to *Lithraea brasiliensis*

Experiments in guinea pigs showed that the animals sensitized to *Lithraea* did not cross react to oleoresins from six other genera of *Anacardiaceae* (*Schinus Schinopsis Mangifera Astronium Semecarpus Pistacia*)

Quantitative patch tests with serial dilution of oleoresin in patients hypersensitive to *Lithraea* showed that the skin reaction produced by the species of *Toxicodendron* are consistently larger than those caused by the species of *Lithraea* Similar results were obtained in experiments delineated to study the primary irritative action of these two genera The irritative action of fresh leaves and oleoresin extracted from green and dried leaves of the three species of *Lithraea* were weaker than than of the genus *Toxicodendron*

SUMMARY

This paper presents some of the peculiarities of the Brazilian flora and which may be of some interest to allergists from other parts of the world

The subject is discussed in nine chapters In the first chapter are describ

ed the substances (seeds, flowers fibers) commonly used for the stuffing of pillows mattresses sofas etc, and which may act as inhalant allergens These substances are derived from different families of plants *(Gramineæ Typhaceæ Trigoniaceæ Compositæ Convolvulaceæ Bromeliaceæ Apocynaceæ, Asclepiadaceæ Bombaceæ)*

The following chapter is devoted to the cultivated grasses of Brazil among wich the most widely distributed species are *Melinis minutiflora Hyparrhenia rufa Panicum maximum Panicum purpurascens* The species *M minutiflora* is the responsible for the only pollen season existent in Brazil

Two chapters are dedicated to the Brazilian species of the families *Compositæ Amoranthaceæ* and *Chenopodiaceæ* The acreage covered by the anemophilus species of these families are not yet great enough to be an important factor in the endemic pollinosis in Brazil

The characteristics of the only pollen season found in Brazil are discussed in another chapter This season which extends from the middle of May to the middle of June is produced by the grass *Melinis minutiflora* Pollinosis is considered a rarity in Brazil and only three typical cases of hay fever have as yet been reported in this country

Three chapters are dedicated to the family *Anacardiaceæ* After giving the distribution of the principal toxi allergenic species of this family in South America and Brazil the Author presented the results of his studies on cross reaction between the allergenic principle of the different genera specially between the genera *Toxicondendron Lithraea Schinus Schinopsis Spondias Mangifera Semecarpus*

RÉSUMÉ

Ce rapport traite de quelques particularites de la flore allergenique du Bresil susceptibles d intéresser les allergologistes des autres parties du monde

Le sujet est traite en neuf chapitres

Le premier chapitre traite des substances (graines fleurs fibres) généralement utilisées pour le rembourrage des oreillers matelas sophas etc et qui peuvent etre des agents allergéniques Ces substances proviennent de differentes familles de vegétaux *(Graminées Thyphacees Trigoniacees Composees Convolvulacees, Bromoliacées Apocynacees Asclepiadacées Bombacees)*

Le chapitre suivant est consacré aux herbacées cultivées au Brésil parmi lesquelles les plus repandues sont *Melinis minutiflora Hyparrhenia Rufa Panicum maximum Panicum purpurascens*

L espece *Melinis minutiflora* est la seule ayant une production saisonniere de pollen au Brésil

Deux chapitres sont consacres aux variétés bresiliennes des familles des *Composees Amaranthacées* et *Chenopodiacées*

La superficie couverte par les variétés anemophilus de ces familles n est pas encore suffisante pour etre un facteur important de l existence des rhumes des foins endémiques au Brésil

Dans un autre chapitre nous étudierons les caractéristiques de la seule saison pollenifère du Bresil Cette saison qui s étend du milieu de mai au milieu de juin est le fait de la seule herbe *Melinis minutiflora* Le rhume des

foins est considéré au Brésil comme une rareté et seulement trois cas typiques de la maladie ont été signalés dans le pays

Trois chapitres traitent des *Anacardiacées* Après avoir indiqué la répartition géographique des espèces toxi allergéniques de cette famille au Brésil et en Amérique du Sud l'auteur rend compte du résultat de ses études sur les réactions croisées entre les principes actifs de ces diverses espèces et essentiellement des *Toxicodendron Lithrae Schinus Schinopsis Spondias Mangifera* et *Semecarpus*

ZUSAMMENFASSUNG

Dieser Bericht enthält einige Besonderheiten der brasilianischen Flora die auch von einigem Interesse für Allergologisten aus anderen Ländern der Welt sein dürften

Dieses Gebiet wird in neun Kapiteln diskutiert Im ersten Kapitel werden die Substanzen besprochen (Samen Blüten Fasern) die gewöhnlich zur Füllung von Kissen Matratzen Sofas etc verwendet werden und die als Inhalationsallergene fungieren können Diese Substanzen stammen von verschiedenen Pflanzenfamilien (*Gramineae Typhaceae Trigoniaceae Compositae Convolvulaceae Bromeliaceae Apocynaceae Asclepiadaceae Bombaceae*)

Das folgende Kapitel ist den kultivierten Gräsern von Brasilien gewidmet von denen *Melinis minutiflora Hyparrhenia rufa Panicum maximum Panicum purpurascens* am meisten verbreitet sind Die Spezies *M minutiflora* ist für die einzige in Brasilien vorkommende Pollen Jahreszeit verantwortlich

Zwei Kapitel sind den brasilianischen Arten der Familien *Compositae Amaranthaceae Chenopodiaceae* gewidmet Die von den Anemophilus Arten dieser Familien bedeckten Ackergebiete sind noch nicht gross genug um ein wichtiger Faktor für die endemische Pollenkrankheit in Brasilien zu sein

Die charakteristischen Merkmale der einzigen in Brasilien vorkommenden Pollen Jahreszeit werden in einem anderen Kapitel besprochen Diese Jahreszeit die von Mitte Mai bis Mitte Juni dauert wird durch die Grasart *Melinis minutiflora* hervorgerufen Pollenkrankheit ist in Brasilien eine Rarität und bisher wurde in diesem Lande nur über drei typische Fälle von Heufieber berichtet

Drei Kapitel sind der Familie *Anacardiaceae* zugedacht Nachdem der Autor einen Ueberblick über die Verteilung der hauptsächlichen toxisch allergenen Arten dieser Familie in Südamerika und Brasilien gegeben hat berichtet er über die Resultate seiner Kreuzreaktionsstudien zwischen den allergenen Bestandteilen der verschiedenen Gattungen hauptsächlich zwischen den Gattungen *Toxicondendron Lithraea Schinus Schinopsis Spondias Mangifera Semecarpus*

RESUMEN

El autor se refiere a algunas particularidades de la flora del Brasil que pueden ser de interes para los alergistas de otros países

El tema es tratado en nueve capítulos En el primero se detallan las sustancias (semillas flores fibras) utilizadas para rellenos de muebles y colchones

que pueden actuar como alergenos inhalantes Esas sustancias provienen de diversas familias de plantas (*gramineæ thyphaceæ trigoneaceæ compositæ convolvulaceæ bromeliaceæ apocynaceæ asclepiadaceæ bombaceæ*)

El capítulo siguiente está dedicado a las gramíneas de cultivo de las cuales las más difundidas son *melinis minutiflora hyparrhenia rufa panicum maximum panicum purpurascens* La especie *melinis minutiflora* es responsable de la unica estación polinica existente en Brasil

Se dedican dos capitulos a las especies brasileras de las familias *compositæ amarantaceæ y chenopodiaceæ* La superficie cubierta por las especies anemófilas de estas familias no es aun suficientemente grande como para tener importancia desde el punto de vista de la polinosis

Las caracteristicas de la unica estación polínica del Brasil se discuten en otro capítulo Esta estación se extiende desde mediados de mayo hasta mediados de junio y es producida por una graminea la *melinis minutiflora* La polinosis debe ser considerada como una rareza en Brasil y hasta la fecha sólo han sido señalados tres casos

La familia *anacardiaceæ* esta tratada en tres capitulos Luego de referirse a la distribución de las principales especies tóxico alergénicas de esta familia en Sud America y Brasil el autor expone el resultado de sus estudios sobre la reactividad cruzada entre los principales generos *toxicodendrum lithraæ schinus schinopsis spondias mangifera semecarpus*

AUSTRALIA

by

C T PIPER

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The continent of Australia extends from the 10th to the 45th parallels of latitude It is a very ancient continent The western five sixths is arid plain country with a minimal rainfall and leached soils on which a desert vegetation supports a scattered population of sheep cattle and wild animals Only comparatively small areas near the southern coast receive sufficient rain to support much population The tropics get heavy seasonal rains but the soil will not hold the water and the country reverts rapidly to unproductive desert as soon as the dry season sets in The eastern sixth of the continent consists of high land rising to 5 000 f very quickly from the Pacific On this littoral and on the Western slopes of the mountains the greater part of the fertile ground and therefore the population is situated European colonisation is generally speaking not more than 150 years old and industrialization not more than 50 years The result of this late development has been a high degree of centralisation and urbanisation The population is European and about 80 % British stock There is a very small aboriginal population remnant of the original nomad race The indigenous animals of Australia are not domesticable and the herbaceous vegetation is not cultivable so that the country itself could never have supported an increasing colonisation unless the colonists had introduced their own food plants and basic economy The Australian economy is therefore a European economy with the same environmental circumstances as the European Allergic problems are therefore European with certain minor adjustments by climate and there are no recognised indigenous allergic problems I have never heard of an allergic disease caused by sensitivity to a native animal Native grass and tree pollens are minimally allergenic One does see occasionally a case of severe contact dermatitis from the inland herbage in very wet seasons These people live hundreds of miles from us and the offending herbage has not been identified As far as I know allergic disease does not occur in the aboriginal race in its native state There are still a few thousands of these people wandering the desert

PRACTICE IN AUSTRALIA

The practice therefore has the same patterns as that of Europe In order to avoid personal impression and give a composite picture I circularised the questionnaire to my colleagues and there is notable agreement in the answers to it

House dust and grass pollen are the common irritants eggs milk wheat nuts and tomatoes are the common food irritants Fungi are uninvestigated but there is an impression that alternaria are guilty on the tropical coasts In my own southern area purely agricultural cladosporium plays an important part in hay fever It is a probable peculiarity of my own locality that the commonest skin reaction is to wheat chaff extract and many of these people react to an intranasal swab Both these reactions are rare in European migrants The area has a summer cover of dry grass for four to six months of the year and such dry grass is the natural summer environment [illegible] The

course of our year our clinics see about 900 referred pollen cases about 1/5 th of our practice This from a population of less than a million The incidence of spring hay fever of all degrees is 7 % Under our system specialists see only those patients with whom family doctors cannot cope It will be noted that about 1 in 200 of the population are referred for specialist treatment for allergy in each year The actual incidence of asthma is about 1 % in adults and about 1 6 % in school children There is no unusual insect allergy and we have no allergenic wasps The possibility of midges and minute flies causing allergic symptoms has never been investigated here I do not know of any case where termites a common insect in Australia have been responsible for trouble Occupational allergy is not important except in regard to pollinosis chaff allergy and occasional cattle and tomato mould allergy in primary producers Wool producers do not suffer allergic disease from their sheep except for an occasional contact dermatitis in the shearers In these cases the irritant is the debris in the wool which remains insoluble after water and ether washing

Otherwise occupational respiratory and contact allergy are as usual in countries where industrial hygiene is by law at high level Diagnostic techniques follow approved North American lines It is generally believed that delayed reactions are not significant I myself think them important in mould allergy and testing for sensitivity to vaccines Skin tests with vaccines are regarded as useless but sub cutaneous testing is used to assess the starting dose of a vaccine treatment There is generally an open mind as to the reality of bacterial allergy but no doubt at all of the value of vaccine hyposensitisation Food tests are regarded variably some do many and some none at all As a food asthmatic I have found them personally valuable generally it is agreed that food tests are helpful when positive especially in children and that negative food tests are of no value I do food tests

in all asthmatics the occasional dramatic success justifi... Elimination diets are regarded as difficult and food diaries as helpful ... difficult

I use intra nasal swabbing as a diagnostic test to confirm ... skin sensitivity is or is not nasal hypersensitivity

Methods of treatment are as usual techniques following ... lines with individual variations on dosages Pollens and house dust ... commonly used. I also use wheat chaff Three men who have excell... its use intradermal methods only I use intradermal propeptan... children and for co seasonal pollen treatment Children are relieved of ... dust symptoms for months by five injections and this is the only ... pollen treatment which helps our patients 50 % get g... results in both cases Most Australian allergists are satisfied with co seasonal treatment by routine minimal extract therapy where antihistamines fail our patients My own area has large plantings of pinus insign... Workers in these forests get a true pine pollinosis There must be heavy exposure over a long time to induce hypersensitivity and symptoms depend on heavy exposure This pollen is said in the books to be non allergenic Our dry climate is probably responsible for heavier exposure than is usual

THE STATUS OF ALLERGY

The Australian Society of Allergists has 40 members Two thirds of them are full time allergists About one to 230 000 of population and one to 400 of practitioners There are Sections of Allergy in the British Medical Association in Victoria and New South Wales each with about 15 members

Medical education in Australia is in the province of the Universities and the right to claim to be a specialist depends on appointment to the Visiting staff of a teaching hospital or the possession of a special degree Allergists are recognized teachers but only one university stipulates that students must attend an allergy clinic Teaching of allergic disease therefore remains in the hands of ...
British pat...
methods ...
allergists failure to produce a concept that fits into the general concepts of medicine Until allergy is rationalised British and hence official Australian medicine will not ...
as ...
pa...
fi...
...ous is demonstrated by the figures given above that one in 200 of the population passes through our clinics each year

SUMMARY

Australia has a European economy and allergic problems are the ones usual to European communities with minor differences of climate There are no indigenous problems of significance or interest The common irritants are the grass pollens house dust cladosporium egg milk wheat and nuts In my area pollinosis affects 7 p 100 and 1 p 100 seek specialist help Asthma occurs in about 1 p 100 of adults 1 6 p 100 of school children There is no unusual insect allergy occupational allergy is very occasional occuring as contact dermatitis in the usual industrial ways and occasionally in primary producers as chaff dust asthma or shearers dermatitis There is no fixed impression on bacterial allergy vaccine hyposensitisation is commonly used and believed to be of great value Diagnostic and hyposensitisation techniques are based on recognized European and American methods Most Australian allergists have studies in both continents Three prominent allergists use intradermal desensitisation only and find it very satisfactory In my own area pine pollinosis certainly exists and cladosporium allergy is very common

The status of allergy The Australian Society of Allergists has 40 members to serve about 10 million people 2/3 rds of these are full time workers There are sections of allergy of B M A in Victoria and New South Wales the members of which are also members of the Society of Allergists

Medical teaching in Australia follows British patterns There is therefore scepticism of allergic methods Allergists are recognized teachers but only one school insists on attendance at allergy clinics Teaching of allergic disease remains the province of the general physicians Until allergy is rationalized so as to fit into the general concept of pathology scepticism of this kind must remain General practitioners and laity however have such confidence in allergic methods that about 2 p 100 of the people are treated in allergy clinics each year

RÉSUMÉ

L economie australienne est du type européen et les problemes concernant l allergie qui peuvent se poser sont ceux des autres communautes europeennes avec quelques variantes mineures dues au climat Il n existe pas de problemes locaux ayant une signification ou un interet particulier

Les allergenes les plus frequents sont les pollens de graminées la poussiere domestique le cladosporium les œufs le lait le ble et les noix

Dans mon district environ 7 p 100 de la population souffrent de pollinose et 1 p 200 des malades font appel aux soins medicaux spécialisés

L asthme se rencontre chez environ 1 p 100 des adultes et 1 6 p 100 des enfants On ne rencontre pas d allergie aux insectes les maladies allergiques professionnelles sont tres rares elles se presentent sous la forme de dermatites de contact comme cela est courant dans l industrie On rencontre aussi de l asthme produit par les poussieres de grains et la dermatite des tondeurs de laine

Il n y a pas de doctrine fixe en matiere d allergie bacterienne On pratique

généralement la désensibilisation avec des extraits allergéniques, qui est considérée comme une thérapeutique de grande valeur.

Les techniques de diagnostic et de désensibilisation [illegible] sur les méthodes ayant fait leurs preuves en Europe et en Amérique. La plupart des allergologistes australiens ont fait leurs études dans le[illegible] du monde. Trois de nos plus éminents spécialistes de l'allergie emp[illegible] sivement les traitements intra dermiques de désensibilisation et [illegible]vent qu'ils donnent toute satisfaction.

Dans la région où j'exerce, on rencontre de la pollinose pro[illegible] qui [illegible] les pins et l'allergie due au cladosporium est très fréquent.

Enseignement de l'allergie. L'Association des allergologistes au [illegible] compte 40 membres pour 10 millions d'habitants; les deux tiers de ces médecins pratiquent exclusivement l'allergologie. Il y a des sections d'allergologie de la B.M.A. à Victoria et dans la Nouvelle Galles du Sud dont les membres sont également de la « Society of Allergists ».

En Australie l'enseignement médical est modelé sur celui de la Grande Bretagne. Il existe donc un certain scepticisme à l'égard des méthodes de l'allergologie.

Le droit d'enseignement est reconnu aux allergistes, mais une seule école médicale considère les cours d'allergologie comme obligatoires. L'enseignement de l'allergologie reste du domaine de la médecine générale.

Jusqu'à ce que l'allergologie ait été rationalisée de manière à s'accorder avec les conceptions de la pathologie générale, un scepticisme de ce genre est appelé à subsister.

Les médecins pratiquant la médecine générale et le public ont cependant une telle confiance dans les méthodes de l'allergologie que 1 p. 200 de la population est soignée annuellement dans les cliniques d'allergologie.

ZUSAMMENFASSUNG

Australien besitzt eine europäische Ökonomie und die allergischen Probleme sind die gleichen wie in Europa, mit geringen klimatisch bedingten Unterschieden. Es gibt keine lokal bedingten Probleme von Wichtigkeit oder Interesse. Die meist irritierenden Stoffe sind die Graspollen, der häusliche Staub, Cladosporium, Eier, Milch, Weizen und Nüsse. In meiner Gegend haben 7 p. 100 der Leute eine Pollinosis und 1 p. 200 Spezialisten helfen. Asthma tritt bei 1 p. 100 der Erwachsenen und 1,6 p. 200 der Schulkinder auf. Es gibt keine ungewöhnliche Insektenallergie. Berufsallergien sieht man nur gelegentlich als Kontaktdermatitis in der üblichen industriebedingten Art und Weise und gelegentlich bei Ersterzeugern als Häckselstaubasthma oder Scherererdermatitis. Es gibt noch keine fixe Vorstellung über eine bakterielle Allergie; meist wird eine Vaccine-Desensibilisierung angewendet und für wertvoll gehalten. Diagnostik und Desensibilisierungsmethoden fussen auf bekannte europäische und amerikanische Methoden. Die meisten australischen Allergologisten haben in beiden Kontinenten studiert. Drei prominente Allergiefachleute verwenden allein die intradermale Desensibilisierung und finden diese sehr zufriedenstellend. In meiner eigenen Gegend gibt es eine sichere Kieferblütenerkrankung und Allergie gegenüber Cladosporium ist recht häufig.

Der Allergiestatus Die australische Allergiegesellschaft zahlt 40 Mitglieder die uber 10 Millionen Menschen betreuen 2/3 von ihnen sind Vollspezialisten Es gibt Allergiesektionen der B M A in Victoria und in Neu Sud Wales deren Mitglieder ebenfalls der Allergiegesellschaft angehoren

Die medizinische Ausbildung in Australien erfolgt nach englischem Vorbild Daher besteht Skepsis uber die Allergiemethoden Allergologisten sind bekannte Lehrer aber nur eine Schule legt Wert auf Besuch von Allergie Kliniken Ueber allergische Krankheiten zu unterrichten bleibt dem Gebiet der praktischen Ärzte uberlassen Solange Allergie als zum allgemeinen Gebiet der Pathologie gehorig betrachtet wird mussen skeptische Momente diesen Fach gegenuber bestehen bleiben Praktische Ärzte und Laien haben jedoch so grosses Vertrauen zu den Allergiemethoden dass uber 1 p 200 der Bevolkerung jedes Jahr in Allergiekliniken behandelt werden

RESUMEN

Australia posee una economia de tipo europeo y los problemas alergicos son semejantes a los de las comunidades europeas con algunas diferencias menores debidas al clima No existen problemas indígenas de significación o interés Los irritantes más comunes son los pólenes de gramíneas polvo domestico Cladosporium huevo leche trigo y nueces En la zona del autor la polinosis afecta al 7 p 100 de los cuales 1 p 200 solicita atencion especializada El asma se presenta en alrededor del 1 p 100 de los adultos y del 1 6 p 100 de los niños en edad escolar No hay alergia a insectos marcada La alergia ocupacional es rara presentándose casos de dermatitis de contacto en la industria y ocasionalmente

No existe una opinión clara sobre la alergia bacteriana la vacunacion con extractos bacterianos se utiliza comunmente y se piensa que es de gran valor El diagnóstico y la desensibilización se realizan con las tecnicas utilizadas en Europa y América habiendo la mayoría de los alergistas australianos estudiado en ambos continentes Tres alergistas eminentes utilizan unicamente la desensibilisación intradérmica con resultados satisfactorios En la zona del autor existe ciertamente polinosis causada por el polen de pino siendo asimismo comun la alergia por Cladosporium

La situacion profesional La Sociedad Australiana de Alergistas cuenta con 40 miembros siendo la poblacion de Australia de unos 10 millones de habitantes De esos 40 los dos tercios se dedican exclusivamente a las enfermedades alergicas La Asociacion Médica Británica tiene secciones de alergia en Victoria y New South Wales cuyos miembros lo son asimismo de la Sociedad Australiana de Alergistas

La enseñanza medica en Australia sigue las líneas generales de la inglesa Hay por lo tanto escepticismo en los métodos alérgicos Si bien la alergia esta reconocida como especialidad sólo una escuela de medicina incluye obligatoriamente cursos prácticos y la enseñanza está en manos de los medicos generales Hasta tanto la alergia sea racionalizada de manera a incorporarse en el concepto general de la patología este estado de cosas continuará El medico general y la poblacion tienen sin embargo tal confianza en los metodos alérgicos que alrededor del 1 p 200 de la poblacion se atiende anualmente en los servicios de alergia

ARGENTINA

por

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ENFERMEDADES ALERGICAS Y CAUSAS

La Republica Argentina es un país situado entre 21° 46 55 y 66° 12 35 de latitud sur tiene une población de 20 000 000 de habitantes aproximadamente con practicamente igual numero de hombres y mujeres Hay predominio de descendientes de españoles italianos e indígenas Dos tercios de la población viven en zonas urbanas y más del treinta por ciento vive en grandes ciudades La cuidad de Buenos Aires y sus alrededores contiene más de la cuarta parte de la población total del país o sea más de 5 000 000 de habitantes Hay 19 ciudades con mas de 100 000 habitantes

La densidad es de 11 habitantes por km en relación con la superficie habitable y de 7 km² con relación al total La superficie del país es de 2 800 000 km² Hay toda clase de climas condicionados por su geografía alta montaña meseta llanura desierto y costas marítimas Hay grandes rios navegables Hay zona sub tropical templada fria y polar

El hombre ha creado riqueza agricola y ganadera modificado la flora espontánea y condicionado la formación de extensas zonas de flora alergógena principalmente de *gramíneas quenopodiaceas amarantaceas* y *compuestas* Hay intensas epidemias de polinosis por

— *Lolium multiflorum poa annua cynodon dactylon*
— *Ambrosia tenuifolia*
— *Chenopodium spp Kochia scoparia Salsola kali (var) tragus*
— *Amaranthus quitensis*

Entre los árboles los que causan mayor numero de enfermos son

— *Acer negundo*
— *Platanus spp*
— *Celtis spinosa*

Las epocas del año con epidemia de polinosis son aproximadamente

— *Arboles* julio agosto
— *Gramíneas* noviembre diciembre

— *Compuestas* febrero marzo
— *Amarantaceas* febrero marzo
— *Quenopodiaceas* febrero marzo

En las ciudades situadas en las cercanías de los grandes ríos que condicionan gran humedad ambiente hay endemias de alergia por hongos anemófilos y parasitantes Los que más frecuentemente producen alergia respiratoria son los esporos de

— *Aspergillus spp*
— *Alternaria spp*
— *Penicillum spp*
— *Hormodendrum spp*
— *Mucor spp*
— *Rhizopus spp*

De los hongos parasitantes los que mayor numero de casos de alergia provocan son

— *Candida albicans*
— *Trichophyton spp*
— *Epidermophyton spp*
— *Microsporum spp*

La ganadería fuente de riqueza en las zonas de llanura crea frecuentes problemas de rinitis y asma alergicos por epitelios de vacunos y equinos principalmente La población de ciudades no acostumbra convivir con perros y gatos de ahí que no haya encontrado una frecuencia digna de ser mencionada

De los alergenos inhalantes domesticos el que mayor numero de enfermos causa es el *polvo de casa* Su frecuencia es extraordinaria Hay muchos enfermos por *plumas de aves* pero su utilización como relleno de almohadas y acolchados no es tan frecuente como en otros países de ahí que no constituya un problema numerico importante Los rellenos se hacen frecuentemente con *paina* y *lana* a pesar de lo cual no hay gran cantidad de enfermos causados por estas subtancias lo mismo puedo decir de *algodon* y *seda* Hay zonas del país donde se cosecha algodón y otras muy extensas en donde se cría ganado lanar y hay importantes fábricas de industrialización de la lana y el algodón pero no hay estadísticas suficientes sobre numero de enfermos alergico como consecuencia de esas actividades

El país ha comenzado a industrializarse intensamente en los ultimos años lo que ha hecho aumentar el numero de enfermos por alergia ocupacional e industrial del tipo respiratorio y cutáneo La inexistencia de estadísticas hechas por alergistas o medicos del trabajo con experiencia hace imposible una valoracion numérica que destaque la importancia del problema que considero grande y creciente

No hay información numerica suficiente sobre alergia por insectos como alergenos inhalante Hay poca casuistica sobre alergia por picadura de abejas hormigas y mosquitos

No hay problema de *rhus toxicodendrum* aunque hay plantas de accion parecida

Es muy frecuente alergia alimenticia por

— harina de trigo
— leche de vaca
— huevo de gallina

— papa
— naranja

Es muy frecuente alergia bacteriana por
— Staphylococcus aureus
— Streptococcus pyogenes
— Escherichia coli
— Salmonellas
— Hemophilus influenzae
— Klebsiella pneumoniae

No hay síndromes alérgicos típicos de la Argentina Las características clínicas los alergenos culpables los sexos y edades de las personas afectadas no presentan diferencias dignas de ser tenidas en cuenta con respecto a las descripciones hechas en otros países No hay estadísticas suficientes para poder informar sobre cantidad de enfermos sexos edades preferencias intensidades y orden de frecuencia de cada síndrome Solamente puedo informar que la incidencia de alergia clínica es semejante a la de los países que cuentan con parecida configuración geográfica flora fauna agricultura ganadería industrias y características étnicas de la población

Los síndromes alérgicos más frecuentes y los tipos de alergenos que los provocan son
— *Rinitis* por *polvo de casa polenes alimentos gérmenes*
— *Asma* por *alimentos hongos gérmenes drogas polvo de casa*
— *Eczema* por *alimentos drogas hongos gérmenes cosméticos*
— *Toxemia* por *alimentos drogas*
— *Urticaria* por *alimentos drogas parásitos gérmenes*
— *Cefaleas* por *alimentos drogas gérmenes*
— *Gastropatías* por *alimentos drogas*
— *Enteropatías* por *alimentos drogas*

DIAGNOSTICO

El diagnóstico de las afecciones alérgicas se hace según las normas y técnicas comunes en todos los países que cuentan con alergistas experimentados En la Argentina hay dos sistemas en general para las pruebas cutáneas el de escarificación y el intracutáneo Algunos utilizan el primero pero los más utilizan el segundo La mayor parte de los alergistas argentinos a tiempo completo o tiempo parcial han estudiado en los E E U U o son discípulos de los que allí estudiaron de ahí que haya predominio de las técnicas norteamericanas

Los extractos que se utilizan en los mejores servicios de alergia se fabrican con las técnicas recomendadas en los E E U U Las concentraciones varían según los criterios de los alergistas Personalmente y casi todos mis discípulos entre los que se cuentan diez jefes de servicios de alergia utilizan las pruebas intracutáneas extractos en solución acuosa con solución Buffers fenolada al 4 p 100 en concentraciones adecuadas y distintas para pólenes hongos inhalantes domésticos y alimentos Para polvo de habitación utilizamos el método de dilución volumétrica Para los otros el sistema de unidades Stull Cooke y Coca (nitrógeno proteico y nitrógeno total)

Hacemos pruebas cutáneas con alimentos pero pocas y solamente con los mas frecuentemente ingeridos Siempre se indican dietas de prueba Se tiene en cuenta tanto a los alimentos con prueba cutánea positiva como a los que dieron prueba cutánea negativa

Damos importancia a las pruebas cutáneas immediatas y tardías con micro organismos patógenos En alergia bacteriana damos más valor a la prueba cutánea inmediata y en alergia de infección damos más valor à la prueba cutánea tardía

No hacemos «tests» de rutina Seleccionamos Solamente hacemos pruebas cutáneas para confirmar las sospechas surgidas de un exhaustivo interrogatorio hecho por medicos alergistas y no por enfermeros o ayudantes Las pruebas cutaneas sirven para confirmar un diagnóstico sospechado y valorar la probable intensidad de sensibilización así como para iniciar el tratamiento de hiposensibilizacion Las pruebas clinicas de reexposicion se hacen cuando son necesarias

Hay en la Argentina alergistas que hacen «tests de rutina y tambien hay quienes dan la máxima importancia a las pruebas cutaneas con alimentos

Las pruebas cutáneas de «parches son utilizados para los casos en que se sospechan eczema o dermatitis por contacto Los medicos de fabrica han comenzado a utilizarla frecuentemente

Las pruebas de transmision pasiva y otras son utilizados excepcional mente con fines de investigación en laboratorios altamente especializados

TRATAMIENTO

Los alergistas argentinos con buena formacion en alergia hacen el trata miento que corresponde a cada circunstancia clinica Se utiliza adrenalina antihistaminicos y corticoides para el tratamiento sintomático

Para el tratamiento profilactico se aconseja evitar la respiración ingestion o contacto con el alergeno causal y si esto no es posible la desensibilizacion específica con la técnica correcta de dosis e intervalo adecuados por la via subcutánea en caso de polinosis hongos inhalantes y germenes Para polinosis se prefiere en general el tratamiento pre estacional y el co esta cional La exclusion de alimentos alergicos se hace por largos meses en forma absoluta El tratamiento con suspensiones de germenes muertos se hace por largos meses en forma continuada

Con Martorelli utilizo desde hace años para los enfermos de polinosis que viven lejos de centros urbanos el tratamiento por vía per lingual con buen resultado Intentamos asi resolver el problema de los tratamiento con extractos de pólene en zona rurales en las que no hay medicos con idoneidad suficiente en alergia

ALERGISTAS Y SU FORMACIÓN

No hay estadística en la Argentina sobre numero de medicos especiali zados en alergia bien sea a tiempo completo o parcial tampoco es posible informar sobre relacion con el numero total de medicos

Hay alergistas en las grandes ciudades solamente Las ciudades que no son capitales de provincia solo excepcionalmente tienen alergistas

Tengo referencias de alergistas a tiempo completo en solamente 5 ciudades de las que la menor tiene aproximadamente 300 000 habitantes En ellas hay solamente de 1 a 3 alergistas a tiempo completo Hay muchos medicos que atienden enfermos alergicos pero no son alergistas y no han recibido entrenamiento adecuado Es imposible calcular su numero El fracaso de sus tratamientos implica gran descredito para la especialidad En la ciudad de Buenos Aires hay aproximadamente quince alergistas a tiempo completo para una población de más de cinco millones de habitantes Hay muchos a tiempo parcial pero es imposible precisar cuántos y muchos más que hacen tratamientos denominados anti alérgicos sin que en realidad lo sean Se limitan a tratamientos inespecificos

Hay en la Argentina dos sociedades de alergia con caracter nacional No hay sociedades regionales El numero de medicos asociados no llegan a cien en cada una de ellas La mayoría son alergistas a tiempo parcial Las reuniones cientificas son anuales o mensuales segun el numero de comunicaciones cientificas las que en general son pocas

Una de las sociedades ha realizado Jornadas de Alergia y la otra «Congresos de Alergia» Algunos medicos pertenecen a las dos sociedades pero la mayoría pertenece solamente a una u otra Las actividades de una y otra sociedad son totalmente independientes

No existe obligacion universitaria para los estudiantes de medicina de seguir cursos sobre alergia En algunas universidades en los ultimos años se dan conferencias y demostraciones prácticas con asistencia obligatoria Se hacen en servicios de alergia en hospitales El tiempo que se utiliza es de pocas horas para cada estudiante

Se dictan cursos para medicos en el Departamento de Graduados de la Facultad de Medicina de Buenos Aires desde hace quince años sobre alergia clinica y polinosis No son obligatorios constan de 15 a 20 horas de enseñanza teórica y practica en un servicio de alergia por las mananas Se da certificado de asistencia pero no título de Alergista No se toma examen de competencia Hace pocos meses en las Universidades de la Plata Cordoba y Rosario se han iniciado actividades semejantes En el Curso de Fisiopatologia de la Nutrición para medicos dietologos y dietistas hay dos Bolillas sobre alergia En Buenos Aires otros alergistas han dictado tambien cursos para graduados sobre alergia clinica En los programas de materias clinicas y de higiene para estudiantes de medicina hay *temas* de alergia de enseñanza teórica

Puede inscribirse en los cursos de graduados cualquier medico que presente su titulo habilitante y pague el derecho arancelario Debe concurrir al 80 p 100 de las clases teóricas y prácticas

El publico de las grandes ciudades esta tomando actualmente una actitud comprensiva y coopera en el esfuerzo de los alergistas Se han creado servicios de alergia en los más importantes hospitales de la ciudad de Buenos Aires y de las capitales de las provincias El publico busca ahora al alergista sin necesidad de que se lo aconseje su medico de cabecera

Es lástima que el publico siga creyendo que solamente es alérgico el que estornuda La ilustración popular sobre alergia es muy elemental y se limita a la rinitis alergica en su casi totalitad Muchos médicos toman una actitud esceptica y pesimista con respecto a la alergia Peor aun escriben sobre alergia sin saber lo que e

medicos y más aun, profanos creen que lo más importante en alergia es hacer «tests» cutáneos Se quejan de que los tratamientos son muy prolongados y costosos y que los resultados no compensan los costos de tiempo y dinero

PROBLEMAS

Los problemas de orden médico que la alergia plantea en la Argentina son de índole asistencial educacional y preventiva Hay pocos especialistas a tiempo total o parcial Hay muchos que hacen tratamientos sin suficiente experiencia Hay pocos establecimientos especializados en el diagnóstico y tratamiento específicos Hay confusion y pesimismo en los médicos pediatras clínicos y de especialidades sobre las ventajas de la investigación de alergenos y el tratamiento específico Hace falta una adecuada educación sanitaria de las poblaciones y una enseñanza universitaria más intensa a los estudiantes de medicina así como mayor numero de cursos en los departamentos de graduados de las Facultades de Medicina del país Se necesita urgentemente una extensa intensa y permanente campaña de medicina preventiva haciendo enfasis en la solucion correcta de los síndromes alérgicos mínimos en los exámenes en salud y periodicos que se realizan en los centros de salud hospitales maternidades dispensarios etc

La medicina rural en la Argentina necesita una organización adecuada Son prácticamente inexistentes en el país medicos rurales con un mínimo de experiencia en tratamientos específicos de alergia y manejo de extractos alergénicos Solamente saben hacerlos pocos medicos en pocas grandes ciudades Poblaciones de más de 100 000 habitantes no tienen ni un solo medico con alguna experiencia en la práctica de alergia

Hasta que no haya un cuerpo medico suficientemente entrenado en alergia clinica no tendremos estadísticas dignas de ser tomadas en cuenta Es por eso que en este trabajo no doy información estadística No la hay

Con excepcion de unos pocos servicios de alergia en las grandes ciudades no se hace profilaxis de la alergia La immensa mayoría de los enfermos recibe tratamiento sistemático no específico Los antihistamínicos y los corticoides son ampliamente utilizados así como los antibioticos ademas de la vieja medicación adrenalina calcio aminofilina vacunas etc

RESUMEN

La Republica Argentina tiene una poblacion de 20 000 000 de habitantes aproximadamente en una superficie de 2 800 000 km² Hay toda clase de climas altas montañas llanura desierto y costas marítimas Hay grandes ríos navegables Hay zona sub tropical templada fría y polar Las plantas mas alergógenas son *lolium multiflorum poa annua cynodon dactylon ambrosia tenuifolia chenopodium spp kochia scoparia salsola kali* (var) *tragus amaranthus quitensis acer negundo platanus occidentalis y celtis spinosa* Los meses del año con epidemias de polinosis son julio y agosto

(árboles) noviembre y diciembre (gramíneas) febrero y marzo (compuestas amarantáceas y chenopodiadeas)

Hay también endemias y epidemias por hongos anemófilos *Aspergillus alternaria penicillum hormodendron mucor* y *rhizopus*

Hay gran cantidad de enfermos por *polvo de casa plumas de aves epitelios de mamíferos drogas* y *alimentos* (harina de trigo leche de vaca huevo de gallina papa citrus)

Es muy frecuente la alergia bacteriana y de infección

No hay síndromes alérgicos típicos de la Argentina No hay estadísticas suficientes para informar sobre cantidad de enfermos y orden de frecuencia de cada síndrome Puede sin embargo considerarse que la incidencia de alergia clínica es semejante a la de los países que cuentan con parecida configuración geográfica flora fauna agricultura ganadería industrias y características étnicas de la población El diagnóstico y el tratamiento son realizado con las técnicas comunes a otros países Los alergistas con experiencia prefieren el método de prueba cutánea intradérmica y el tratamiento específico El tratamiento sintomático es sin embargo el único que utilizan gran cantidad de médicos sin suficiente formación en alergia Hay pocos alergistas y pocos que enseñen alergia, en relación con la población del país

Los problemas más importantes que la alergia plantea en la Argentina son de índole asistencial educacional y preventiva Hay confusión y pesimismo entre los médicos como consecuencia de haber fracasado al intentar hacer tratamiento mediante extractos alergénicos sin suficientes conocimientos técnicos Muy lentamente el público va formando opinión adecuada sobre alergia Hacen falta intensas campañas de educación sanitaria La medicina rural en lo referente a alergia carece de centros de alergia adecuados Los pocos servicios de alergia del país están en las grandes ciudades y son insuficientes para las necesidades de las poblaciones

RÉSUMÉ

La République Argentine a une population de 20 000 000 d habitants et une superficie de 2 800 000 kilomètres carrés On y rencontre toutes sortes de climats et de contrées des hautes montagnes des plaines des régions désertiques et des côtes maritimes Il y a de grands fleuves navigables On trouve des zones subtropicales froides et polaires

Les plantes allergéniques y sont le *Lolium multiflorum* le *Poa annua* le *Cynodon dactylon* l *Ambrosia tenuifolia* le *Chenopodium spp* la *Kochia scoparia* la *Salsola Kali* (var) le *Tragus* l *Amaranthus quitensis* l *Acer negundo* le *Platanus occidentalis* et le *Celtis spinosa*

Les mois de l année pendant lesquels se produisent les epidémies de pollinoses sont juillet et aout (arbres) novembre et decembre (graminées) février et mars (Composacées Amarantacées Chenopodiacees) On observe aussi des epidémies et des endémies causées par les moisissures *Aspergillus Alternaria Penicillum Hormodendron Mucor* et *Rhizopus*

Il y a beaucoup de cas d allergie respiratoire imputables à *la poussière domestique aux plumes d oiseaux aux phanères de mammifères aux médicaments et aux aliments* (farine de blé lait de vache œufs patates agrumes)

L allergie d origine infectieuse et bactérienne est tres frequente Il n y a pas de syndromes particuliers à l Argentine On peut dire sans hesitation que les incidences de l allergie clinique sont les memes que celles des autres pays ou se rencontrent une meme configuration geographique une meme flore une meme faune une meme agriculture et un meme elevage des industries et des caracteristiques semblables

Les methodes de diagnostic et de traitement sont celles couramment employees dans les autres pays

Les allergologistes experimentes préferent la methode des tests cutanes intra dermiques et les traitements specifiques

Cependant le traitement symptomatique est le seul utilisé par de nombreux médecins qui manquent de formation allergologique suffisante Il y a peu d allergologistes en Argentine par rapport au nombre des habitants et peu d entre eux enseignent l allergologie

Les problemes que pose l allergie en Argentine sont d un ordre thérapeutique éducationnel et préventif Il regne une certaine confusion et un certain pessimisme parmi les medecins par suite de l echec des traitements à base d *extraits allergènes employés par des praticiens ne* possedant pas les connaissances techniques necessaires

Tres lentement le public se forme une opinion juste sur l allergie Le manque de campagne de propagande sanitaire se fait sentir Les médecins ruraux qui s interessent à l allergologie manquent de centres allergologique appropriés

Les peu nombreux services d allergologie existants se trouvent dans les grandes villes et sont insuffisants pour les besoins de la population

SUMMARY

The Republic of Argentina has a population of 20 000 000 inhabitant and a surface of 2 800 000 square kilometers There are various climates and various types of countries high mountains plains deserts and sea coasts There are large navigable rivers sub tropical cold and polar zones

Local allergenic plants are *Lolium multiflorum Poa annua Cynodon Dactylon Ambrosia tenuifolia* (Ragweed) *Chenopodium Kochia scoparia Salsola Kali* (var) *Tragus Amaranthus quitensis Acer Negundo Platanus occidentalis* and the *Celtis spinosa*

The months during which epidemical pollinosis occurs are July and August (Tree pollen) November and December (grasses) February and March (Composae Amarantacae Chenopodiacae)

Endemical and epidemical allergic diseases due to the following moulds also occur *Aspergillus Alternaria Penicillum Hormodendrum, Mucor* and *Rhizopus*

Many allergic disturbances are caused by *house dust feathers hair* and *dander drugs* and *foods* (wheat flour cow milk eggs sweet potatoes citrus fruits)

Allergy caused by microbian and infectiou agents is very often met with There are no typical syndroms in Argentina

The clinical incidence of allergy is the same as in other countries where

similar conditions prevail geographical flora fauna agricultural cattle breeding and industries

Diagnose and treatment processes are the same as those usually employed in other countries

Trained allergologists prefer the intradermic testing process and the specific treatments Nevertheless a great number of physicians lacking sufficient allergological training only employ the symptomatic treatment method

Allergologists are scarce in Argentina when compared to the number of its inhabitants and few ones teach allergology

Allergic problems in Argentina are therapeutical educational and preventory ones

A certain confusion and pessimism are felt among physicians towards allergy they are the consequence of failures of treatments with allergenic extracts employed by physicians lacking the necessary technical training Very slowly the public is gaining a better knowledge of allergic questions We suffer from the lack of actively conducted sanitary propagande campaigns Countrydoctors interested in allergy have no available specialized centers

The few existing allergological departments are only found in larger cities and cannot meet with populations requirements

ZUSAMMENFASSUNG

Die Republik Argentinien besitzt eine Bevolkerung von 20 Millionen und umfasst eine Gesamtoberflache von 2 800 000 Quadratkilometer Man trifft hier alle moglichen Klima— und Landschaftsarten hohe Gebirge Ebenen Wustengegenden Kustenlandstriche Es gibt grosse schiffbare Flusse Man trifft hier subtropische kalte und polare Klimazonen vor

Allergenpflazen sind *Lollium multiplorum Poa annua Cynodon dactylon Ambrona tenuifolia Chenopodium spp Kochia scoparia Tragus Amaranthus quintensis Acer negundo Platanus occidenthalis* und *Celtis spinosa*

Die Monate in denen Pollinose Epidemien auftreten Juli und August (Arbus) November und Dezember (Graser) Februar und Marz (Compo saceae Amarantaceae und Quenopodiaceae) Epidemien und Endemien durch Pilze verursacht *Aspegillus Alternaria Penicillium Hormodendron Mucor* und *Rhizopus*

Es gibt viele Krankheitsfalle die auf folgende Ursachen zuruckzufuhren sind *der hautliche Staub Vogelfedern Saugetierepithelien Medikamente* und *Nahrungsmittel* (Weizenmehl Kuhmilch Huhnereier Patate Citrus fruchte)

Eine durch Infektionen und Bakterien verursachte Allergie kommt sehr haufig vor Es gibt fur Argentinien keine speziellen Syndrome Man kann mit gutem Gewissen behaupten dass die Merkmale der klinischen Allergie mit denen in jenen Landern ubereinstimmen die eine gleiche geographische Konfiguration die gleiche Flora dieselbe Fauna dieselbe Art von Ackerbau und Viehzucht ahnliche Industrien und andere gemeinsame Merkmale haben

Die Methoden der Diagnostik und Behandlung stimmen mit denen in den anderen Landern überein

Die Allergologieforscher bevorzugen den Intracutan Test und die spezifische Behandlung

Indessen wird von vielen Ärzten die keine genugende Allergie ausbildung haben einzig und allein die symptomatische Therapie angewandt Es gibt im Verhaltnis zur Einwohnerzahl nur sehr wenig Allergologisten und nur sehr wenige unter ihnen halten Vorlesungen uber die Allergologie

Die von der Allergie aufgeworfenen Probleme sind in Argentinien therapeutischer erziehrischer und praventiver Natur Es besteht unter den Ärzten eine gewisse Verwirrung und auch Pessimismus hervorgerufen durch das Versagen der auf Allergenen Extrakten beruhenden Therapie die von Ärzten mit fehlenden technischen Kenntnissen angewendet wurde

Sehr langsam bekommt die Allgemeinheit nun eine wahre Vorstellung uber die Allergie Das Fehlen von Propaganda Aktionen macht sich fuhlbar bemerkbar Der sich fur Allergologie interessierenden Landmedizin fehlt es an *geeigneten Allergologiezentren*

Die wenigen Allergologieabteilungen befinden sich in den grossen Stadten und reichen fur die Gesamtbevölkerung keineswegs aus

ITALIE

par

U SERAFINI *et* U DI NARDO

(Istituto di Patologia Medica Università di Firenz Italia)

Les travaux effectues au cours de ces dernières annees dans differents pays sur l allergie du point de vue medico social tout en n etant pas très nombreux prouvent de façon evidente l importance toujours plus grande de ce probleme particulier

Il faut souligner tout d abord que ce probleme toujours a l étude peut etre envisage sous des aspects tres differents et apparait comme tres complexe

Étant donne l etendue du sujet et le peu de temps qui nous est assigne nous nous bornerons dans cet expose à envisager simplement certains aspects du probleme cependant suffisants pour mettre en lumiere parti culierement dans notre pays l importance de l allergie du point de vue médical et social

Pour poser correctement les termes du probleme il est avant tout nec s saire de reunir avec soin les nombreuses donnees statistiques present nt un interet social et de proceder a leur elaboration en tenant compte des connais sances actuelles sur l aspect clinique et biologique des phénomenes aller giques

I DONNÉES STATISTIQUES

a) *Mortalite* — Le releve des cas de mort dus aux affections considérees comme cliniquement allergiques montre tout d abord qu ils representent *1 24 0 roo du nombre total des deces (voir* Tableau I)

comme tres significatif dans ce sens (*bronchite chronique cardiopathies* tumeurs)

Dans le cadre des affections allergiques l on remarque que les pointes asthme bronchique » Ce n est œdeme de Quincke » « urti ies allergiques non spécifiées »

TABLEAU I

Causes de mort dues à des formes morbides sur un total de 481 911 décès — Année 1951

CAUSE	CAS DE MORT	SUR LE NOMBRE TOTAL DES DÉCÈS
Affections allergiques	5 984	1 24
Bronchite chronique	7 055	1 46
Cardiopathies valvulaires	15 866	3 29
Tumeurs	50 773	10 53

L'on vérifiera cette affirmation par l'examen des données rapportées dans le tableau II se référant aux années 1951 1954 (*)

TABLEAU II

Décès causés par des affections allergiques sur un total de 481 911 cas — Années 1951 54

ANNÉE		ASTHME BRONCHIQUE	ŒDÈME DE QUINCKE	URTICAIRE	ECZÉMA allergique	DIVERS
1951	Hommes	3 458	2	1	2	41
	Femmes	2 465	4	1	—	10
	Total	5 923	6	2	2	51
1952	Hommes	3 558	2	—	1	36 (**)
	Femmes	2 454	4	1	1	10 (*)
	Total	6 012	6	1	2	46
1953	Hommes	3 990	2	—	1	[illegible]
	Femmes	2 854	3	—	—	7
	Total	6 844	5	—	1	28
1954	Hommes	2 805	2	—	—	32
	Femmes	1 847	1	—	—	10
	Total	4 652	3	—	—	42

(*) Dont 30 par favisme
(**) Dont 8 par favisme

Si l'on examine la proportion de la mortalité par rapport au sexe, l'on verra que celle des hommes l'emporte légèrement (environ 58,7 p. 100 des cas).

Vu l'importance exceptionnelle prise par l'« asthme bronchique » parmi les

(*) Nous avons jugé opportun de limiter notre étude à cette période, étant donné que seulement en 1951 l'on a appliqué la Classification Analytique Internationale adoptée à Paris en 1948 aux données statistiques.

causes de mort dues à des affections allergiques nous avons cru bon d exa miner en detail (voir tableau III et graphique 1) les donnees concernant la

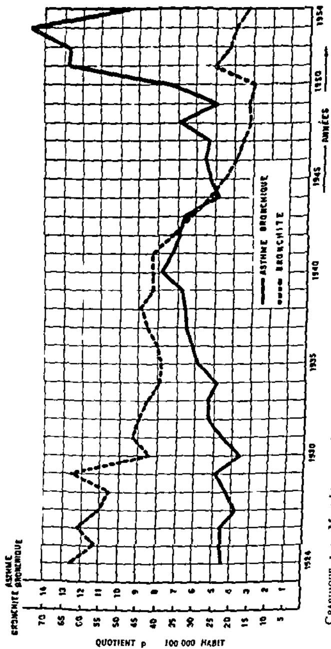
TABLEAU III

Mortalite par asthme bronchique et par bronchite en Italie au cours de la periode 1924 1954

ANNÉE	POPULATION (millions)	NOMBRE TOTAL de décès par asthme bronchique	QUOTIENT pour 100 000 hab	NOMBRE TOTAL de décès par bronchite	QUOTIENT pour 100 000 hab
1924	38 7	1710	4 4	24 096	62 3
1925	39 1	1805	4 6	22 141	56 6
1926	39 4	1775	4 5	23 875	60 6
1927	39 8	1525	3 8	21 913	55 0
1928	40 1	1732	4 3	20 978	52 3
1929	40 5	1990	4 9	25 290	62 4
1930	40 9	1477	3 6	17 136	42 0
1931	41 1	1880	4 6	18 99	46 2
1932	41 6	2242	5 4	18 73)	45 0
1933	41 9	2261	5 4	17 854	42 6
1934	42 2	2107	5 0	16 653	39 4
1935	42 6	-459	5 8	16 484	38 7
1936	42 9	2673	6 2	17 151	40 0
1937	43 2	27 3	6 4	18 412	42 6
1938	43 6	2833	6 5	19 128	43 9
1939	44 0	2902	6 6	18 049	41 0
1940	44 4	3885	7 6	18 464	41 6
1941	44 8	3248	7 2	18 5 2	41 3
1942	45 0	3125	6 8	16 214	36 0
1943	44 3	2880	6 5	3 908	31 4
1944	44 5	2117	4 7	1 354	-5 5
1945	44 7	2286	5 1	9 999	2- 3
1946	45 0	2492	5 5	8 633	19 2
1947	45 3	2479	5 4	865	17 3
1948	45 7	3054	6 7	7 198	15 7
1949	46 0	2191	4 8	7 127	15 5
1950	46 3	3443	7 4	6 722	14 5
1951	47 0	5923	12 7	1 612	24 7
1952	47 2	6012	12 7	10 173	21 5
1953	47 5	6884	14 4	9 335	9 6
1954	48 2	4652	9 4	8 139	6 8

mortalite due a l asthme bronchique en Italie au cours des trente annees 1924 1954 D apres l examen de ces données il ressort que la mortalité imputable a cette cause n a fait qu augmenter dans le temps et cela soit qu on envisage les chiffres dans un sens absolu soit par rapport a l ensemble de la population Le nombre des déces varie en effet entre un minimum de 1 477 cas (1930) et un maximum de 6 884 cas (1953) et le quotient pour 100 000 habitants entre 3 6 (1930) et 14 4 (1953)

La repartition des cas de déces par *asthme bronchique* dans les differentes regions d Italie telle qu elle decoule de l examen du tableau IV montre que le plus haut pourcentage est atteint dans le Frioul Venétie et en Ligurie



Graphique 1. — Mortalité par asthme bronchique et par bronchite en Italie au cours de la période 1924-54.

TABLEAU IV

Mortalité par asthme bronchique dans les différentes régions d'Italie par rapport à l'ensemble de la population — Année 1951

RÉGION	POPULATION (en millions)	NOMBRE DE DÉCÈS	QUOTIENT POUR 100 000 habitants
Piémont	3,53	529	14,9
Lombardie	6,50	756	11,6
Trentin Haut Adige	0,73	90	12,3
Vallée d'Aoste	0,37	13	3,5
Vénétie	3,85	504	13,0
Frioul Vénétie Julienne	0,93	160	17,2
Ligurie	1,57	276	11,5
Emilie	3,51	442	13,5
Toscane	3,16	396	12,5
Ombrie	0,80	79	9,8
Marches	1,34	212	15,8
Latium	3,37	340	10,0
Abruzzes	1,60	234	14,0
Campanie	4,30	612	14,2
Pouilles	3,18	389	12,2
Basilicate	0,61	68	11,1
Calabres	1,97	211	10,7
Sicile	4,42	516	11,6
Sardaigne	1,26	97	8,4

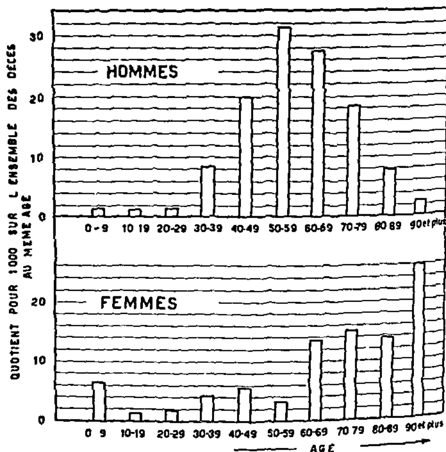
TABLEAU V

Nombre des décès par asthme bronchique par rapport à l'âge et au sexe — Année 1951

AGE	NOMBRE ABSOLU	QUOTIENT POUR [illegible] 000 sur l'[illegible] des décès au même âge	NOMBRE DES DÉCÈS [illegible]
		HOMMES	
0-9	34	1,48	22 958
10-19	4	1,27	3 146
20-29	12	1,93	6 187
30-39	49	8,65	5 663
40-49	241	20,10	11 964
50-59	635	31,59	20 153
60-69	952	27,73	34 330
70-79	1093	18,48	59 133
80-89	418	8,00	52 226
90 et plus	20	2,39	8 347
		FEMMES	
0-9	22	6,32	3 479
10-19	7	1,52	4 600
20-29	14	1,98	7 045
30-39	37	4,22	8 759
40-49	91	5,84	15 571
50-59	245	3,24	75 515
60-69	632	13,56	46 594
70-79	980	14,97	65 421
80-89	410	13,78	29 752
90 et plus	27	25,28	1 068

alors que les pourcentages les plus bas se retrouvent en Val d Aoste et en Sardaigne

L importance de la mortalité due a l asthme bronchique par rapport a l âge (pour l annee 1951 voir le tableau V) a été envisagee par nous en nous rapportant non pas a la population vivante mais au nombre de déces suivant les differents groupes d age Le tableau V et le graphique 2 nous per



GRAPHIQUE 2 — Nombre des deces par asthm bronchique par rapport a l age et au sexe (1951)

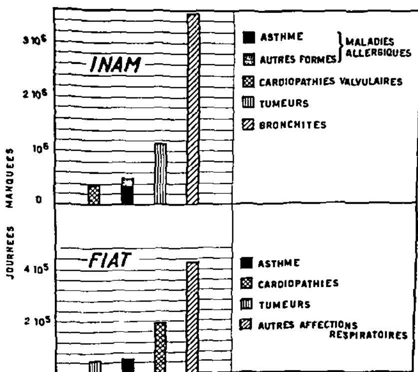
mettent d affirmer chez les hommes un pourcentage maximum de mortalité dans la 6e decade Chez les femmes au contraire les pointes les plus elevees se rencontrent a partir de la 7e décade

Le total des deces reste constamment plus éleve chez les hommes que chez les femmes

TABLEAU VI

Repartition de certaines maladies dans l ensemble des 5 865 553 sujets inscrits a L I N A M (Année 1954)

MALADIE	NOMBRE des cas	POURCENTAGE h l suj t x mi és (5 865 553)	POURCENTAGE ch z j ts su vi l n quement (2 859 411)	JOURNÉES d malad e	DURÉE MOYENNE d l ess stan (n de jours)
Cardiopathies valvulaires	11 078	0 19	0 38	373 603	33 72
Tumeurs	28 922	0 49	1 01	1 129 881	39 07
Maladies allergiques	30 761	0 52	1 07	491 509	15 98
Bronchites	269 046	4 59	9 40	3 542 177	13 17



GRAPHIQUE 3 — Journées de tra a l m nquées su vant la malad e (1954)

b) *Morbidite* — Afin d apporter une contribution valable au difficile probleme de l importance des affections allergiques en Italie nous avons cru bon de nous servir des données fournies par un des plus importants organismes d assistance sociale de notre pays l « Istituto Nazio nale Assistenza Malattia (INAM) » Ces données que nous rapportons dans le tableau VI nous permettent de conclure que l incidence des affections allergiques a ete de 0 52 p 100 pour un total de 5 865 553 d inscrits et de 1 07 p 100 sur l ensemble des affections diagnostiquées chez 285 9411 assistes

Dans le tableau VI nous avons egalement cru opportun de comparer l incidence des affections allergiques par rapport a celle d autres maladies d une importance sociale certaine De cette comparaison il apparait que la frequence des affections allergiques est plus grande que celle des cardio pathies valvulaires ou des tumeurs malignes Plus des deux tiers des malades frappes d affections allergiques souffraient d asthmes bronchiques

c) *Pertes economiques et sociales* — Nous avons envisage cet autre aspect du probleme en notant d une part le nombre de journees de travail manquées par les differentes categories de travailleurs (*) et d autre part celui des hos pitalisations dans des etablissements publics ou prives (**)

TABLEAU VII

Journees de travail manquées suivant la maladie
(I N A M — Annee 1954)

MALADIE	JOURNÉES MANQUÉES	POURCENTAGE DE CHAQUE MALADIE pour l ensemble des 46 630 000 journées de travail manquées
Maladies allergiques		
— asthme bronchique	333 263	0 71
— autres formes	158 246	0 34
— total	491 509	1 05
Cardiopathies valvulaires	373 609	0 80
Tumeurs	1 12) 881	2 42
Bronchites	3 542 177	7 59
Idem — Usines Fiat — Année 195 (pour 2.1 298 journées de travail manquées au total)		
Asthme bronchique	5 397	2 43
Cardiopathies	19 408	8 77
Tumeurs	5 111	2 30
Bronchites et autres affections respiratoires	43 589	20 80

(*) « Istituto Nazionale Assistenza Malattie (INAM) et Fiat (se tion auto mobile)

(**) Ces données sont celles publiées par l Istituto Centrale l Statistica

Journées de travail manquées. — L'examen du tableau VII et du graphique n° 3 fait clairement apparaître l'importance que revêt l'asthme bronchique considéré comme cause d'absence du travail, même en le considérant par rapport à d'autres maladies.

Un aspect particulier de ce problème consiste dans *la fréquence de ces formes morbides dans les différentes catégories professionnelles*.

Le tableau VIII prouve que l'incidence de l'asthme bronchique est plus

TABLEAU VIII

Fréquence des cas d'asthme bronchique dans différentes catégories de travailleurs (I.N.A.M. — Année 1954)

CATÉGORIE	N° DES TRAVAILLEURS	N° DES CAS D'ASTHME BRONCHIQUE	POURCENTAGE
Industrie	3 364 419	14 489	0 43
Commerce	528 862	1 625	0 30
Agriculture	1 972 272	4 771	0 24

TABLEAU IX

Fréquence des cas d'asthme bronchique chez des travailleurs répartis suivant les catégories professionnelles (I.N.A.M. — Année 1954)

CATÉGORIE	N° DE OUVRIERS	N° DES CAS D'ASTHME BRONCHIQUE	FRÉQUENCE POUR 1 000 OUVRIERS
Ports	8 368	118	14 1
Industries chimiques	147 597	828	5 6
Industries du verre	37 752	210	5 5
Mines	44 547	245	5 4
Textiles	81 086	984	5 4
Textiles synthétiques	21 104	07	5 0
Industries agricoles de l'alimentation	69 169	340	4 [illegible]
Ouvriers des transports	61 553	302	4 [illegible]
Bâtiment	840 563	3 963	4 7
Tanneries	18 746	85	4 5
Céramique	28 612	126	4 4
Carrières	58 799	250	4 2
Industries mécaniques et métallurgiques	663 593	2 755	4 1
Lin, chanvre, jute	30 275	113	3 7
Papier	48 971	176	3
Laine	92 676	317	3 4
Soie	56 056	192	3 4
Transports automobiles	47 293	151	3 1
Bois	157 308	463	2 [illegible]
Chaussures et cuir	64 485	186	2 [illegible]
Typographie	46 487	121	2 [illegible]
Matières plastiques	15 081	34	2 2

TABLEAU X

Malades hospitalises dans des hôpitaux et dans des etablissements prit es par age et par sexe classes d apres la raison de leur hospitalisation

CAU E DE L HOSPITALISATION	AGE (années)										
	0 10	11 20	21 30	31 40	41 50	51 60	61 70	71 80	81 90	I lus	Total
					HOMMES						
Pollinose	3	8	5	4	2	3	1	3	—	—	29
Asthme bronchique	293	143	179	251	563	868	656	292	45	8	3 298
Œdème de Quincke	20	15	12	9	14	12	9	2	1	—	94
Urticaire	49	29	34	47	34	15	10	5	2	—	225
Eczema allergique	22	12	34	46	58	48	44	13	4	—	281
Autres formes	87	40	56	44	58	22	14	7	3	—	331
									Total général		4 258
					FEMMES						
Pollinose	5	3	7	7	6	3	2	3	—	—	36
Asthme bronchique	161	101	217	347	537	638	521	243	42	2	2 809
Œdeme de Quincke	12	11	10	10	13	9	11	7	—	—	83
Urticaire	34	22	55	36	42	25	11	3	—	—	228
Fczéma allergique	26	20	21	20	53	38	35	15	—	—	228
Autres formes	51	28	52	31	33	29	12	6	2	—	244
									Total genéral		3 628
									Total de tous les malades		7 886

TABLEAU XI

Nombre des malades hospitalisés dans des hôpitaux et dans des établissements privés répartis suivant la durée de l'hospitalisation (Année 1954)

Cause de l'hospitalisation	Journées d'hospitalisation									
	1-4	5-7	8-10	11-15	16-20	21-30	31-60	61-90	Plus	Total
Pollinose	9	17	14	6	6	5	6	1	216	65
Asthme bronchique	365	470	719	1010	816	1158	1 071	273		6107
Œdème de Quincke	40	21	30	33	22	13	15	3		177
Urticaire	105	118	96	47	26	35	17	4		453
Eczéma allergique	17	52	92	113	71	77	75	7		509
Autres formes	104	117	123	77	49	57	36	3		575
							Total des journées			7 886

TABLEAU X

Malades hospitalises dans des hôpitaux et dans des etablissements prives par age et par sexe classés d apr s la raison de leur hospitalisation

CAUSE DE L HO PITALISAT ON	AGE (années)										
	0 10	1 20	2 30	31 40	4 50	5 60	61 70	71 80	81 90	Plus	Tot l
	HOMMES										
Poll nose	3	8	5	4	2	3	1	3	—	—	29
Asthme bronch que	293	143	179	251	563	868	656	292	45	8	3 298
Œdeme de Qu ncke	20	15	12	9	14	12	9	2	1	—	94
Urt ca re	49	29	34	47	34	15	10	5	2	—	225
Eczéma allerg que	22	12	34	46	58	48	44	13	4	—	281
Autres formes	87	40	56	44	58	22	14	7	3	—	331
Total général											4 258
	FEMMES										
Poll nose	5	3	7	7	6	3	2	3	—	—	36
Asthme bronch que	161	101	217	347	537	638	521	243	42	2	2 809
Œdème de Qu ncke	12	11	10	10	13	9	11	7	—	—	83
Urt ca re	34	22	55	36	42	25	11	3	—	—	228
Eczéma allerg que	26	20	21	20	53	38	35	15	—	—	228
Autres formes	51	28	52	31	33	29	12	6	2	—	244
Total général											3 628
Total de tous les malades											7 886

insuffisance cardiaque (voir Lenegre et coll 1950) (décompensation ventriculaire droite aigue ou chronique) ou d une *reaction anormale aux médicaments* pouvant etre mise en rapport soit avec l action toxique de certains d entre eux (morphine Jimenez Diaz Feinberg Unger Serafini etc sympathicomimétiques Hamburger et coll Blamoutier et Claude etc) soit avec les réactions anaphylactiques qu ils peuvent engendrer et qui peuvent amener plus ou moins rapidement une issue fatale (nous rappelons à ce sujet le choc anaphylactique provoqué par la pénicilline le sérum l iode l A C T H etc)

Il faut à notre avis assigner une place particuliere a cette sensibilite aux medicaments bien souvent sous estimée ou meconnue étant donne que souvent elle peut devenir un des facteurs responsables de l augmentation de la mortalite par asthme bronchique que l on rencontre a l heure actuelle A cet egard il faut egalement tenir present que les traitements avec des dérives synthétiques de la cortisone surtout s ils sont prolongés peuvent entrainer chez l asthmatique des complications liees non seulement à l hyper corticisme mais aussi a un blocage de la cortico surrenale avec es graves consequences surtout au moment ou le traitement est arreté (syndrome de suspension) Exception faite du role favorisant de certains médicaments il nous semble d apres des observations personnelles qu il existe des cas ou *independamment de l administration* de medicaments la maladie presente une allure particulièrement grave aboutissant en peu de temps a la mort

Dans une recherche que nous avons effectuée dans la litterature sur des cas d asthme mortels et soumis a un controle anatomo pathologique (Rackemann Hamburger et Dubois de Montreynaud Walton et coll Bullen Williams Houston et coll Westermeyer et coll etc) nous avons essaye de préciser le nombre des sujets dont la mal die a presenté une issue fatale rapide en considérant comme telle une mort qui s est verifiée d ns un maximum de deux ans après le début de l affection Dans ce sens sur 57 cas d asthme a issue fatale nous avons relevé que 17 presentaient cette evolution (pour ce qui concerne l age il faut remarquer que si la plupart des malades étaient ages de quarante a soixante ans d autres avaient des âges tres divers comme le soulignent aussi Williams et Bullen)

Nous désirons attirer l attention des chercheurs sur le fait que l asthme bronchique qui parfois présente des le début une symptomatologie grave qui repond peu aux therapies courantes et qui mene a une issue rapidement mortelle (independamment du moins en apparence d autres facteurs etiologiques ou de complications) manifeste un caractere particulier de « malignite » Plus exactement les malades dont l asthme prend cette allure tres differente de celle que pre ente habituellement l maladie peuvent etre considéres comme atteints d une forme d asthme particulier et que l on peut d un point de vue clinique définir comme forme à évolution maligne (ou asthme malin)

Nous nous rendons par ailleurs compte que pour pouvoir parler avec certitude d une forme clinique tout a fait différenciee il faudrait pouvoir l étayer sur des bases anatomo pathologiques ou alors sur un mécanisme étiopathogénique que nous sommes actuellement dans l impossibilité de fournir

Tout en fais [illegible]

ne pouvons en parler que sous l aspect des observations cliniques et pour mieux préciser l idée plus générale qui se trouve exprimee dans les locutions « asthme grave » « asthme mortel » « asthme compliqué » nous pensons qu il est utile d envisager le probleme et de le mettre également en discussion dans le but de susciter des recherches tendant a mettre en lumiere les causes qui interviennent pour provoquer cette « malignité » Ce n est que sur la base de ces recherches qui doivent etre conduites dans differentes directions et en tenant compte du terrain individuel (importance des alterations éventuelles du systeme neurovegetatif de troubles endocriniens disharmonies de la surrenale — d apres Lunedei) des conditions individuelles du systeme respiratoire et cardio vasculaire et d eventuelles autres causes d issue fatale (en particulier la périartérite noueuse rencontree bien que rarement par Harkavy Rackemann Turiaf malignisation angio mesenchymateuse Jimenez Diaz et Arjona) qu il est possible que l on parvienne a séparer une « forme a evolution maligne » avec tous les caracteres d une affection clinique autonome

L etude de la *morbidité des affections allergiques* en Italie met en evidence en premier lieu leur grande diffusion Les chiffres rapportes plus haut (0 52 p 100 et 1 07 p 100 voir tableaux) sont comparables a ceux rapportes dans les statistiques d auteurs d autres pays (0 5 p 100 pour les allergopathies Rackemann 0 5 p 100 pour l asthme Derbes) et apparaissent comme superieurs a ceux rapportes pour les cardiopathies valvulaires et les tumeurs malignes

En ce qui concerne le probleme fort complexe des causes de la morbidite sans entrer dans le domaine des facteurs individuels (constitution facteurs hereditaires âge sexe) qui ne different pas en Italie des autres pays il nous semble opportun d appeler l attention meme brievement sur les facteurs qui déterminent avec le plus de frequence des manifestations d ordre allergique en Italie

Dans un groupe de 10 941 sujets allergiques examinés par nous (entre l année 1931 et l année 1955) nous avons rencontre une reponse positive aux reactions cutanees (*) par différents allergenes particulierement par inhalation dans 5 565 cas (51 p 100 des cas) Parmi les malades qui ont presente une réaction cutanee positive 2 219 (39 p 100) presentaient cette cuti positivité vis a vis de pollens isolés ou associes à d autres allergenes Il est peut etre bon de rappeler qu en Italie les causes les plus fréquentes de pollinose sont dues a des Graminées des Urticacees et des Composées Pour ce qui concerne l espece une sensibilisation tres frequente est celle a la *Parietaria officinalis* (Urticacées) (Frugoni et Serafini) Étant donne sa forte diffusion cet allergene prend dans notre pays une importance particuliere vu qu il n est pas frequemment signalé dans d autres pays mediterraneens (en Espagne Alemany Vall en France Panzani Charpin)

En dehors des pollens l on rencontre des sensibilisations a d autres allergenes par inhalation (Frugoni et Serafini)

Quant aux spores fongiques il faut rappeler ici les recherches recentes et tres etendues de Volterrani et Tosco Ces auteurs qui ont etudié la repar

(*) La méthode que nous avons employée habituellement est celle par scarification intégrée par la méthode intradermique

tition dans l atmosphere d [illegible] de T [illegible] ont remarqué que 10 p 100 [illegible] presentaient une réaction [illegible] fongiques dans l ordre de frequence suivant *Epicoccum purpurascens Penicillium expansum Alternaria tenuis Cladosporium herbarum Botrytis cinerea Mucor Mucedo Aspergillus fumigatus Rhodotorula glutinis* etc

D un point de vue professionnel on peut faire etat de certains cas particuliers On a constaté des syndromes cliniques imputables au ver a soie (avec des réactions cutanees et transfert passif (P K) positifs chez des ouvriers travaillant dans des etablissements ou l on emploie le ver a soie (Marconi et coll) de l asthme bronchique chez des individus affectes au travail du ricin (Berto et Bassi Sangiorgi) des manifestations allergiques variees (avec des reactions cutanees positives) ont ete constatees chez des ouvriers travaillant dans une fabrique de penicilline (Maffei et Napolitano) Les dermatites par contact d origine professionnelle ont ete par contre plus fréquemment signalees (streptomycine dérivés de la phenothiazine etc)

III CONCLUSIONS

Les donnees statistiques que nous avon rapportees dans la premiere partie de cet exposé et en particulier la mortalité élevée leur caractere relativement frequent et le dommage ainsi cause a la vie economique collective justifient elles un interet social pour ce genre d affections ? Certainement pas puisque si l on ne se basait que sur ces donnees le chapitre des maladies sociales finirait par s accroitre demesurement (en effet les pneumonies et d autres formes morbides rentreraient automatiquement dans ce groupe)

Les caracteres qui autorisent cependant à classer les affections allergiques parmi les maladies sociales peuvent se resumer dans les points suivants qui mettent en lumiere d une part les consequences nuisibles de ces affections pour la collectivité et d autre part les possibilites d une prophylaxie qui etant donné le genre des maladies peut etre exercee avec profit

1° Les affections allergiques et en particulier l asthme bronchique diminuent considérablement la capacite de travail et la productivite des individus au point que bien souvent ceux ci sont reduits a un etat de veritable invalidite

2° Ces maladies ont une repercussion sur la demographie d une nation pour la double raison qu elles peuvent raccourcir la duree moyenne de la vie de ces malades et qu elles reduisent les possibilites de se marier et de mettre au monde des enfants bien portants

3° Les caractéristiques de ces manifestations morbides permettent d intervenir en temps utile par differentes mesures capables de les enrayer Il est possible d exercer une action préventive non seulement sur les facteurs héréditaires (prophylaxie eugénetique) mais également sur les facteurs « d exposition » en évitant que ces sujets entrent en contact avec des allergenes particuliers ce qui entrainerait une plus grande possibilité de sensibilisation

C est également a la prophylaxie qu il revient de reeduquer les asthmatiques par differents moyens à savoir un traitement médical approprié

l hospitalisation du malade dans une clinique spécialisée l orientation de ce malade vers une activité sédentaire ou tout au moins proportionnée aux capacités réelles des differents cas

4° Les formes déclarees de ces affections peuvent etre utilement combattues par le *diagnostic precoce* et par une *therapie adequate*

Il serait bon de confier les mesures prophylactiques le diagnostic précoce et la thérapie a des cliniques des centres hospitaliers ou des services spécialises lesquels pourvoiront d autre part a faire de l éducation professionnelle (cours de specialisation vulgarisation etc)

Si l on tient compte des arguments que nous avons énumérés le problème des affections allergiques s avere comme du plus haut intéret social et doit faire l objet de l attention non seulement des chercheurs mais également des autorités et des organisations chargees de veiller sur la santé publique

Il existe en Italie dans toutes les grandes villes des centres d allergie spécialises non seulement aupres des hopitaux mais dans les cliniques privees ou il est possible de faire faire le diagnostic et de se soumettre aux traitements desensibilisants specifiques d apres les techniques habituelles

L importance du probleme de l allergie n échappe pas à l opinion publique italienne comme cela est prouve par le développement de la « Societa di Allergologia » qui a dans Folia Allergologica » son organe officiel Bien qu un véritable enseignement d allergologie reconnu par l État n existe pas encore dans de nombreuses Universites des specialistes font des cours sur ce sujet

Il y a donc en Italie des organismes pour le traitement préventif et pour le traitement thérapeutique des affections allergiques S il est vrai qu a l heure actuelle ils ne sont pas encore tres efficaces il est egalement vrai que dans un plan de lutte contre les affections allergiques l on doit s employer a les valoriser a les compléter de façon a les mettre au service de tous les malades

Le probleme social des affections allergiques pour etre resolu demande encore un travail considérable et qui doit etre effectué avec l aide des organisations d État des organisations sociales et privees

Pour conclure nous pouvons affirmer qu il s agit la d un très grave probleme qui pour ses repercussions sur la vie des peuples demande a etre affronte d urgence et qui avec le concours des organisations nationales et internationales specialement qualifiees pourra tres heureusement s acheminer vers sa solution

RÉSUMÉ

Dans cet expose les auteurs examinent tout d abord les données statistiques relatives a la mortalité à la morbidite et aux charges économiques et sociales dues aux affections allergiques Dans le nombre total de déces la mortalité due aux affections allergiques représente 1 24 p 100 la cause principale etant l asthme bronchique (le quotient varie entre 3 6 et 14,4 pour 100 000 habitants) Parmi les autres maladies allergiques les auteurs

signalent le favisme (38 cas mortels en 1952) Les affections allergiques interviennent pour 0 52 p 100 chez 5 865 553 sujets examinés et pour 1 07 p 100 chez 2 859 414 sujets atteints de maladies diverses Le montant des pertes de travail a été calculé sur la base des journées de travail manquées ainsi que sur le nombre de malades hospitalisés dans les établissements publics et privés

D après des observations personnelles et aussi sur la base des données recueillies dans la littérature il existe des formes d asthme bronchique qui présentent dès le début une symptomatologie grave qui résistent aux thérapeutiques courantes et qui aboutissent rapidement a la mort (quelques mois a deux ans) Il s agit d une forme d asthme particulière que les auteurs définissent comme « forme a évolution maligne » ou « asthme malin » Cependant il n est pas encore possible d affirmer sur la base de ces observations cliniques qu il s agit d une forme clinique autonome et de nouvelles recherches sont nécessaires pour préciser les causes qui interviennent dans cette « malignité » de l asthme

En se référant a la morbidité des affections allergiques les auteurs mentionnent les divers allergènes responsables des manifestations allergiques en Italie Ils rapportent les résultats des examens pratiqués chez 10 941 allergiques (examinés entre 1931 et 1955) et chez lesquels on a vérifié une réaction cutanée positive à diverses substances et plus particulièrement a des pneumallergènes (51 p 100 des cas) 38 p 100 de ces derniers ont montré une réaction cutanée positive aux pollens (isolés ou associés a d autres allergènes) Les auteurs rappellent la fréquence de l allergie a la *Parietaria Officinalis* en Italie ainsi que certains aspects professionnels de l allergie par inhalation A propos de ces données statistiques les auteurs soulignent les caractères particuliers de ces affections (prophylaxie diagnostic précoce thérapie) et mettent en valeur le grand intérêt social des maladies allergiques

Les auteurs examinent enfin brièvement la situation actuelle de l allergie en Italie du point de vue médico social et concluent que le problème des affections allergiques mérite la plus grande attention non seulement de la part des savants mais aussi celle des autorités et des organisations chargées de veiller au maintien de la Santé Publique

SUMMARY

The authors present in this report statistical data concerning the mortality morbidity and the economical and social strain due to allergic affections

Death from allergic disease represents 1 24 p 100 the principal cause being asthma (the quotient varies between 3 6 and 14 4 for 100 000 inhabitants) Among causes of death the authors indicate favismus (38 mortal cases in 1952) Out of 5 865 553 individuals studied 0 52 p 100 are affected with allergic conditions while 1 07 p 100 of 2 859 414 are affected with various other diseases The amount of the total financial loss has been calculated on the base of workless days and on the number of patients hospitalized in public and private clinics

According to personal observation and also on the ground of the data reported in literature there are forms of bronchial asthma which from the start are clinically severe resisting to current treatments and terminating

usually by death (several months to two years) This variety of bronchial asthma is named by the authors as ' malignant asthma However it is not yet possible from the clinical observations to affirm that it is a clinical autonomous form of asthma and new investigations are necessary to define the causes which bring malignancy to this variety of asthma

Refering to the morbidity of allergic disease the authors mention the different allergens responsible for allergic troubles in Italy They report the results of tests practised on 10 941 allergic patients (surveyed between 1931 and 1955) amongst whom was obtained a positive skin test to different allergens most specially inhalants (51 p 100 of the cases) 38 p 100 of the cases showed a positive skin test to pollens (alone or associated with other allergens) The authors relate the frequency of allergy to *Parietaria Officinalis* in Italy and also certain aspects of occupational allergy due to inhalants In relation with the statistical data the authors emphasize the particularities of allergic disease (prophylaxis importance of early diagnosis therapy) and lay stress on the great social importance of allergic diseases

Finally the authors study the critical situation of allergic education and tuition in Italy and conclude that the allergic diseases deserve the most careful attention not only among scientists but also among the authorities and the social State Organisations in charge of the Public Health

ZUSAMMENFASSUNG

In diesem Beitrag berichten die Autoren zuerst uber statistische Daten bezuglich der Mortalitat Morbiditat und der sozialen und okonomischen Schaden [illegible]

Von c [illegible]

100 aus [illegible]

schwankt fur 100 000 Personen zwischen 3 6 und 14 4) Unter anderen allergischen Krankheiten heben die Autoren den Favismus hervor (38 Todesfalle im Jahre 1952) Allergische Manifestationen kommen bei 0 5- p 100 von 5 865 553 untersuchten Personen vor und ebenso bei 1 07 p 100 von 2 859 414 Personen mit den verschiedensten Krankheiten Der Arbeitsverlust wurde auf der Basis der verlorenen Arbeitstage und der Anzahl der in privaten und offentlichen Krankenhausern aufgenommenen Patienten kalkuliert

Nach personlichen Erfahrungen und auch nach Berichten in der Literatur besteht eine von Anfang an mit schweren Symptomen einhergehende Form des Bronchialasthmas die resistent gegen jegliche Therapie ist und schnell zum Tode fuhrt (einige Monate bis zu 2 Jahren) Es handelt sich hier um eine Sonderform des Asthmas die die Autoren als Form mit bosartiger Entwicklung oder malignes Asthma benennen wollen Indessen war es noch nicht moglich auf Basis dieser klinischen Beobachtungen festzustellen ob es sich hier um eine eigene klinische Erscheinung form handelt und neue Untersuchungen sind notwendig um die bei dieser Malignitat intervenierenden Grunde aufzudecken

Indem sie sich auf die Morbiditat der allergischen Affektionen berufen geben die Autoren einen Ueberblick uber die in Italien fur allergische Manifestationen verantwortlichen Allergene Sie berichten uber die Resul

tate der Untersuchungen von 10 941 Allergikern (zwischen 1931 und 1955 untersucht) und bei welchen man eine positive Hautreaktion gegen diverse Substanzen und besonders gegen Pneumallergene (51 p 100 der Falle) durchfuhren konnte 38 p 100 der letzteren Falle zeigten eine positive Hautreaktion gegen Pollen (isoliert oder vermischt mit anderen Allergenen) Die Autoren berichten uber die Haufigkeit der Allergie gegen *Parietaria Officinalis* sowie uber gewisse Aspekte einer Berufsallergie durch Einatmen in Italien Aufgrund dieser statistischen Daten unterstreichen die Autoren die besonderen Merkmale dieser Affektionen (Prophylaxie Diagnostik Vorbeugung Therapie) und betonen das grosse soziale Interesse der allergischen Krankheiten

Die Autoren untersuchen schliesslich noch kurz vom Standpunkt der Sozialmedizin aus die heutige Situation der Allergie in Italien und schliessen daraus dass das durch allergische Erkrankungen bedingte Problem sowohl der grossten Aufmerksamkeit von Seiten der Wissenschaftler als auch der offentlichen Behorden und Wohlfahrtsorganisationen bedarf

RESUMEN

En su exposición los autores examinan primeramente los *datos estadísticos* sobre mortalidad morbidez y perjuicios económicos y sociales debidos a las afecciones alérgicas en Italia

Desarrollan luego *consideraciones de orden medico biologico* y llaman la atención sobre las cifras particularmente importantes de muertes por asma bronquial En lo que respecta al problema de la mortalidad por asma bronquial y en base a observaciones personales y a la literatura los autores toman en consideracion una forma de «evolucion maligna» o «asma maligno» En cuanto a la morbidez de las afecciones alérgicas indican los alergenos responsables más frecuentes

En sus *conclusiones* se refieren además de los datos estadísticos a otros aspectos de estas enfermedades (profilaxia diagnóstico precoz terapéutica) que ponen en evidencia el gran interes social del problema

Finalmente los autores examinan brevemente la situación actual médico social de la alergia en Italia y concluyen que el problema planteado por las enfermedades alérgicas merece toda la atención posible no solamente de parte de los estudiosos sino también de parte de las autoridades y organizaciones dedicadas a la conservación de la salud publica

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YOUGOSLAVIE

par

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L accroissement des manifestations allergiques en Yougoslavie aussi bien que dans les autres pays devient inquiétant D apres les donnees de l Institut Fédéral de Sante Publique de la R P F de Yougoslavie en 1954 dans les hopitaux de ce pays 2 430 asthmatiques et 1 567 malades atteints d autres affections allergiques ont ete hospitalises pendant un total de 52 996 jours La meme annee dans les ambulances de la Securite Sociale il a été traite pour l asthme et d autres manifestations allergiques 6 893 membres du service actif avec 150 202 jours de conge pour maladie En general en 1954 on a traité pour des maladies allergiques 89 233 travailleurs actifs ou des membres de leurs familles ce qui represente une perte de 1 036 794 200 dinars non compris les individus non affilies a la Sécurité Sociale ce qui eleverait cette somme à un total d environ 2 000 000 000 de dinars par an

De toutes les maladies allergiques l asthme est la plus fréquente 510 p 1 000 puis l eczema 181 p 1 000 les urticaires 133 p 1 000 la rhinite allergique 92 p 1 000 et le rhume des foins 18 p 1 000 les allergies alimentaires 28 p 1 000 les migraines 25 p 1 000 et les autres manifestations allergiques 13 p 1 000 (1) L asthme et l eczema apparaissent le plus frequemment pour la premiere fois au cours des premières années de la vie (1) comme l ont constaté egalement Lesne et Dreyfus Sée (2) Wittich (3) Diaz (4) Pasteur Vallery Radot (5) Danilović (6) et d autres pour diminuer ensuite sensiblement de la 3e à la 5e année puis réapparaitre dans un pour centage plus elevé apres la 17e annee à l âge des occupations professionnelles (v fig 1)

Les données citées ne representent que les valeurs moyennes car tout comme S Feinberg l a exposé pour les États Unis d Amérique (7) en Yougoslavie aussi les conditions climatiques et géographiques différentes les conditions économiques et sociales diverses suivant les régions le fait que certaines contrees aient été soumises pendant de longues périodes à l influence de civilisations differentes ont fait que les maladies allergiques se manifestent tout differemment suivant les régions de notre pays

Au point de vue des manifestations allergiques la région la plus défavorable

de Yougoslavie est la Voivodina (Srem Banat et Bačka) avec 3 5 p 100 d asthmatiques et 23 p 100 d allergies en général La Voivodina est une plaine basse (82 86 m d altitude) inondable fertile faisant partie de la

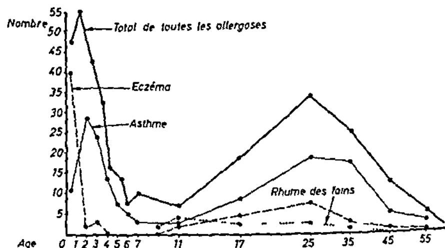


FIG 1 — Rapport entre la premiere apparition d une maladie allergique et l age

plaine pannonienne (fig 2) Dans cette contree exposee pendant des siècles à l influence de la civilisation occidentale l agriculture et l industrie sont tres développées L alimentation de la population y est tres bonne

L état de l allergie est tout à fait rare dans les régions montagneuses du Sud de la Serbie (1 000 2 500 m d altitude), ou il n y a que 0 4 p 100 d asthme et 3 p 100 d autres maladies allergiques Dans ces pays d elevage plus pauvres la plupart des habitants ont encore un mode de vie patriarcal leur alimentation est legère lacto végetarienne avec de la viande seulement de temps en temps et principalement en hiver ils sont maigres sveltes vigoureux et résistants C est le meme cas dans les regions montagneuses du Montenegro de l Herzégovine et de la Macédoine Dans les autres parties de la Serbie dans la Croatie la Bosnie il existe des transitions entre ces deux extremes La population du littoral dalmate au climat mediterraneen longtemps sous l influence de la civilisation romaine ou la nourriture est legere presente pourtant assez de maladies allergiques bien que le climat exerce une action favorable sur les manifestations allergiques des habitants des autres regions La Slovenie contree subalpine avec de vastes forets riche en precipitations atmospheriques avec de frequents brouillards une industrie développée, une alimentation satisfaisante est moins favorable aux asthmatiques

Comme on peut le voir les conditions locales sont donc d une importance particulierement grande et dans des regions differentes elles changent le role de certains facteurs d allergisation C est ainsi que dans les régions montagneuses sèches ou l air est pur plus pauvre en bactéries et ou les gens acclimates aux changements atmospheriques sont resistants l *infection* ne joue pas ce role qu elle a dans les régions basses L influence des *conditions d hygiene des habitations*, qui ont une action pendant toute la vie est égale

ment différente suivant les regions Elles dépendent non seulement du matériel avec lequel les maisons sont bâties de la disposition des pieces mais aussi de l humidité du logement de l encombrement du mobilier des



FIG 2 — Regions asthmogenes de Yougoslavie
Les régions en noir sont les plus défavorables pour les asthmatiques Les régions rayées sont moins défa orables Celles en blanc les plus favorables

conditions d hygiene des cours environnantes etc Dans les regions industrielles certaines *industries* (cuirs ricin soies et autres) sont une cause importante de manifestations allergiques surtout si les conditions de travail n y sont pas satisfaisantes Ces industries agissent tout comme les bactéries ou l infection non seulement par leurs allergenes mais en meme temps par d autres facteurs qui aident la sensibilisation la constitution du tissu de choc et qui augmentent l hypersensibilité des effecteurs Enfin *la civilisation* elle meme influe différemment suivant les regions Dans les regions du Nord ayant une industrie développée et un nombre plus important de grandes villes son influence est manifeste La vie moderne influe sur l accroissement des allergies avant tout par l augmentation constante des allergenes (médicaments produits cosmétiques produits divers ajoutés aux vivres ou conserves alimentaires afin de leur donner un gout une couleur un aspect une conservation meilleure etc) ensuite par la viciation de plus en plus forte de l air surtout dans les grands centres industriels par la tension perpétuelle du systeme nerveux et les continuels « stress » Dans les localités

de montagnes reculees et paisibles ou la vie est encore assez patriarcale ces conditions defavorables n existent pas Enfin par l accroissement des maladies allergiques dans une region le role de l *hérédité* change aussi

Comme nous le voyons donc les conditions locales sont d une enorme importance dans l apparition des manifestations allergiques

CAUSES DES MANIFESTATIONS ALLERGIQUES

En Yougoslavie divers syndromes rentrent dans le cadre de l allergie L asthme est chez nous dans 60 p 100 des cas de nature allergique (8) et maintenant que les tests cutanés sont exécutés avec une série plus complete d allergenes le pourcentage d asthme allergique atteint jusqu a 72 p 100

De meme que Pasteur Vallery Radot (9) Gernez Rieux (10) Diaz (5) Bruun (11) l ont observe dans leur pays respectif, en Yougoslavie également c est a *la poussiere* que l hypersensibilite est la plus frequente Sur 4 216 individus testes au cours des examens faits dans differentes régions de Yougoslavie 1 278 soit 30,3 p 100 étaient sensibilises a la poussiere Cette hypersensibilite a la poussiere est surtout fréquente chez les habitants des régions basses inondables 39 5 p 100 (12) ayant une terre fertile et beaucoup de poussiere tandis qu elle est plus rare parmi les habitants des regions montagneuses 4 6 p 100 (13) La sensibilisation à la poussiere de maison dépend beaucoup des materiaux avec lesquels elles sont construites du *façonnement des murs* des planchers etc du degré d *humidité* de l encombrement des meubles ou d autres choses de l état de ses environs immediats canal souille route poudreuse ou verdure Comme pour les autres allergenes la sensibilisation est aussi influencee par les conditions qui en alterant les muqueuses bronchiques facilitent la pénétration des allergenes et déterminent le tissu de choc Les examens que nous avons faits font ressortir nettement le role des conditions locales Ainsi tandis que parmi les habitants du village de Nemenikuće sur Kosmaj (14) dont les maisons sont situées dans des vallees profondes aupres d un ruisseau et d une mare le pourcentage de sensibilises a la poussiere atteignait 50 p 100 chez ceux dont les maisons se trouvent sur les coteaux continuellement exposees a la circulation de l air pur de la montagne le pourcentage de sensibilises n etait que de 14 p 100

Les cas frequents d allergie latente 10 a 45 p 100 (15) dans lesquels les tests cutanes sont positifs sans que la presence de l allergene correspondant ne provoque de manifestations allergiques et ou l état de *sensibilisation* cesse le plus souvent sans que ces manifestations ne surviennent montrent bien que la sensibilisation seule n est pas suffisante pour que des manifestations allergiques se produisent mais que sont necessaires encore d autres facteurs qui renforcent l hypersensibilite du tissu de choc [Auer (16) Klinge (17) Pasteur Vallery Radot (18) Halpern (19) Blamoutier Biozzi Benacerraf] ou des organes effecteurs [Tiffeneau (20 21) Wolfromm (-)]

L hypersensibilité aux *insectes attaquant les céréales* et surtout à Calandra Granaria est frequente en Yougoslavie 25 3 p 100 tout comme Diaz (5) l a aussi indique pour l Espagne et d autres pays agricoles L allergene peut etre la poudre provenant des ecailles des ailes dessechées de ces insectes

(Morichau Beauchant) (23) ou encore les déjections des insectes (V Spoujitch P Vukasović et I Spoujitch) (24)

Dans notre pays l hypersensibilité est encore frequente aux *moisissures* 13 5 p 100, surtout dans les régions basses inondables ou même dans des localités d altitude quand les maisons situées dans des vallées encaissées sont humides 17 5 p 100 (25) En Voivodina ou nous rencontrons le plus souvent l hypersensibilité aux moisissures ce sont ordinairement les suivantes qui entrent en consideration *Penicillium Aspergillus Alternaria Cladosporium Mucor Monilia* etc (26)

L hypersensibilite *aux pollens* est plus rare 4 8 p 100 surtout parmi la population rurale si bien qu on se demande si l exposition continuelle a un allergene n amènerait pas a l immunisation comme I aroche et ses collaborateurs (27) l ont constaté expérimentalement pour les allergenes alimentaires L hypersensibilité au pollen du tilleul de l acacia et d autres arbres est plus rare A Belgrade ou beaucoup de rues et boulevards sont ombrages de rangees de peupliers *(Populus alba)* l hypersensibilité est frequente 23 p 100 au pollen de cet arbre (Pujević) (28) tandis qu elle n existe pas dans les autres regions ou il n y a pas de peupliers

L hypersensibilite aux *poils d animaux* est encore plus rare en Yougoslavie 2 p 100 et cela meme dans les regions d elevage de montagnes ainsi que Diaz (5) l a aussi constaté en Espagne Est ce parce que dans ces regions le betail se trouve ordinairement loin des maisons dans la mont gne ou bien est ce que comme pour le pollen l exposition continuelle a un allergene amène a l immunisation ? Dans les villes l hypersensibilité aux poils d animaux est un peu plus frequente Cependant en Voivodina ou les plumes s emploient beaucoup pour la literie oreillers matelas couvre pieds l hypersensibilite aux *plumes* est plus frequente (16 p 100) que dans les autres regions du pays

Nous ne rencontrons pas en Yougoslavie d hypersensibilite a certains pneumallergenes particuliers Cependant nous avons deja expose que les conditions locales rendent frequente l hypersensibilite a un allergéne particulier comme par exemple dans le Banat ou la culture du ri in est importante les tests cutanes aux graines de ricin sont positifs chez 22 p 100 de la population (29) dans une peausserie à Niš (30) l hypersensibilite a la poussiere de la fabrique existe chez 47 p 100 des ouvriers et 15 p 100 du personnel est hypersensible a la oie dans la soierie de Novi Sad (12) L hypersensibilité à la farine au tabac à la primevere a l ursol etc est le plus souvent en rapport avec la profession et les conditions locales Parfois la sensibilisa ion est tres specifique par exemple uniquement aux cocons de vers à soie en Macédoine

L hypersensibili é aux *allergènes alimentaires* que Rosenau et Anderson Guy Laroche (27) Djuričić (31) ont obtenue expérimentalement chez les cobayes dans 25 a 80 p 100 des cas et que Rowe (32) Bickel (33) Pasteur Vallery Radot et Wolfromm (34) constatent aussi fréquemment chez les hommes existe également dans notre pays dans 35 40 p 100 des cas (35) Dans la sensibilisation aux allergènes alimentaires les memes facteurs agissent que dans celle aux pneumallergènes

L abondance de l allergene joue ici encore un role important Dans les regions d élevage la sensibilisation à la viande atteint 28 p 100 au lait 6 p 100 dans les villes au cacao 38 p 100 et au paprika dans le Banat ou

l on en fait grand usage 26 p 100 Certaines conditions particulieres aident a la sensibilisation l hypoacidité les infections ou intoxications intestinales les parasites intestinaux Certains condiments et produits employes dans la préparation industrielle des aliments afin de leur donner un aspect une couleur ou un gout meilleurs et pour leur plus longue conservation jouent un role certain L intervalle d introduction de l allergène a aussi son importance (Rosenau Rowe Bickel Guy Laroche V et I Spoujitch) (36)

La sensibilisation aux allergenes de contact pour laquelle Tzanck et Sidi (37) Charpy (38) W Jadassohn (39) ont trouve qu elle est bien frequente se rencontre souvent chez nous aussi A l Ambulance allergologique de la Clinique dermato vénérologique de la Faculte de Medecine a Beograd (prof Sima Ilić 40) au cours des trois dernieres années sur 17 577 cas de dermatoses il y avait 777 eczémas (4 4 p 100) dont 36 4 p 100 d origine professionnelle 31 p 100 d origine médicamenteuse et 8 p 100 d origine cosmétique L hypersensibilite a la laine au caoutchouc e c existait dans 8 5 p 100 des cas Dans tous ces cas il y avait une hypersensibilite a la terebenthine 143 cas, au savon 128 cas aux sulfamides 118 cas au precipite blanc de mercure 98 cas au bichromate de potasse 81 cas a la novocaine 61 cas a l ursol 48 cas etc Sur 990 ouvriers de la raffinerie de petrole a Rijeka D Jakac (41) a trouve 13 eczemas soit 1 3 p 100 Sur 168 *membres* du personnel des hopitaux de Beograd S Perišić (42) a constate une hypersensibilité à la streptomycine dans 19 p 100 des cas et sur 72 ouvrieres employées a la fabrication des antibiotiques dans la fabrique Galenika les tests cutanés ont ete positifs chez 5 5 p 100 (43)

L hypersensibilité est egalement de plus en plus fréquente aux *médicaments* introduits peroralement ou parenteralement A l Ambulance allergologique de la Clinique interne B de la Faculté de Medecine de Beograd au cours de deux annees sur 2 008 manifestations allergiques 131 cas étaient provoques par l hypersensibilite aux medicaments Le plus grand nombre d entre eux etaient sensibilises a la penicilline 65 cas puis a la streptomycine 21 cas a l aspirine 10 cas aux sulfamides 5 cas etc Il y avait 1 cas sensible a la codéine 1 à la q ... lfate de cuivre 1 au sulfate de fer 1 a P A S ...
Sur 103 malades traites a l ... de Beograd en six mois 70 p 100 (45) etaient sensibilises a ce medicament

L allergie latente est fréquente aussi aux medicaments c est à *dire* que les tests cutanes sont positifs mais que le médicament meme ne provoque pas de manifestations allergiques mais les cas dans le quels les réactions cutanées sont negatives sont aussi frequents bien qu il soit clair que les manifestations allergiques proviennent du medicament en question

Le role de l *infection* qui exerce son action depuis la premiere enfance *puis* pendant toute la vie et qui a deja éte mis en evidence par Castex (46) Diaz (47) Salen (48) Rackemann (49) et d autres auteurs est *aussi dans notre* pays l un des facteurs les plus importants dans l apparition des manifestations allergiques Le role de l infection ou des bacteries est tres varie Comme nous l avons expose avec Danilović (50) les bacteries agissent comme allergenes comme facteurs aidant a la sensibilisation elles influent sur la constitution du tissu de choc et à part cela declenchent les crises (Danilović) (6) Les bacteries comme certains autres allergenes puissants (graines de

ricin etc) sont justement dangereuses parce qu en plus des composants de l allergene elles renferment encore en elles des composants qui contribuent a la rapide sensibilisation et à la constitution du tissu de choc

DIAGNOSTIC

Le diagnostic d une manifestation allergique doit non seulement determiner que cette manifestation est à base allergique et a quel allergene existe l hypersensibilité mais encore quelles sont les conditions qui favorisent les manifestations allergiques A ce point de vue l *anamnese* recueillie soigneusement et habilement est d une grande utilité Les *tests cutanés* sont de la plus grande valeur *meme* si dans bien des cas d allergie latente ils sont positifs sans que l allergene en question ne provoque de manifestations allergiques ou que *parfois les réactions cutanées puissent etre negatives* dans des cas ou il est clair que l allergene en question provoque les manifestations allergiques Sans tests cutanés nous considerons que le diagnostic des manifestations allergiques est incomplet Mais c est pourquoi ces reactions cutanees doivent etre faites avec toute la erie d allergenes prepares avec du materiel provenant de differents milieux et qu elles doivent etre executees et interpretees par des personnes en ayant une grande experience

Au debut nous avons execute les tests cutanes avec les allergenes de la maison Sachsiches Serumwerk de Dresde mais depuis 1947 avec les allergenes prepares a l Institut pour le controle des medicaments de la R P de Serbie (Dr M Lazarević) L extraction des allergenes est faite d apres la méthode décrite par S Feinberg (51) l allergene des bacteries est prepare comme un vaccin ordinaire de toutes le bacteries isolees des organes respiratoires et auxquelles on ajoute des Salmonelles et des Colibacilles Les dilutions des allergenes dependent comme l a expose Feinberg de l allergène meme Pour eviter les fortes reactions il est bon de faire une cutireaction avant de procéder aux intradermo reaction (0 1 0 2 cm³) Sur plus de 120 000 intradermo reactions nous n avon eu de reactions tres graves que dans sept cas deux fois a l allergene des graines de ricin deux fois au pollen une fois au blanc d œuf une fois a l ipecacuanha et une fois au serum de cheval Nou faisons ordinairement les tests cutanes avec les allergenes des bactéries des moisissures de la poussiere de la literie des insectes attaquant les céreales des poils d animaux et suivant les conditions locales avec les autres allergenes qui entrent en consideration dans ce cas Nous n attachons de l importance qu aux reactions cutanees precoces bien que les bacteries ne donnent souvent que des reactions tardives

Dans les cas d allergie de contact nous executons des tests epicutanes avec un petit carré de toile d apres Jadassohn et dans les cas d allergie alimentaire des tests sont realis es avec les allergene alimentaires bien qu ils aient une moindre valeur Les resultats des réactions cutanées sont verifies par des dietes eliminatrices en faisant absorber à dessein les aliments nocifs et par un controle radioscopique d apres Hansen apres l absorption de l allergène correspondant (52)

THÉRAPEUTIQUE

En ce qui concerne la therapeutique des maladies allergiques nous ne pouvons etre encore satisfaits La thérapeutique de certains cas comme celle de certaines collectivites ou de régions ne doit pas etre routiniere mais doit repondre à chaque cas donne Il faut appliquer le traitement le plus tot possible tant que les altérations du tissu de choc et des effecteurs sont fonctionnelles reversibles et guerissables Le traitement et le controle doivent etre longtemps poursuivis les manifestations allergiques pouvant se renouveler meme apres de longues interruptions

Dans le traitement des maladies allergiques nous combinons ordinairement diverses méthodes therapeutiques L *élimination* de l allergene correspondant donne souvent un résultat satisfaisant bien que parfois temporaire Differents *produits symptomatiques* combines à d autres methodes en empechant les manifestations allergiques d apparaitre pendant une plus longue periode calment souvent l hypersensibilite du tissu de choc et des effecteurs si bien que ces manifestations ne se produisent pas, meme en présence de l allergene nocif

La *désensibilisation spécifique* que nous appliquons depuis vingt cinq ans nous a donne sur plus de 600 cas (53 54) un bon resultat dans 48 p 100 de ces cas une amélioration dans 34 p 100 tandis que dans 17 p 100 de ces cas il n y a eu aucun changement Il ne faut effectuer la desensibilisation qu avec tous les allergenes pour lesquels il existe des reactions cutanees nettement positives Les premieres injections de fortes dilutions sont donnees deux fois par semaine plus tard une fois par semaine et les dernieres de la plus forte concentration une fois tous les quinze jours Les injections sont augmentees prudemment surtout les dernières les plus fortes car une augmentation trop elevee peut provoquer des manifestations allergiques Il faut poursuivre le traitement pendant longtemps, regulierement sans interruption Nous entretenons les resultats obtenus par des injections donnees de temps en temps pendant un an et davantage Les resultats sont meilleurs si la désensibilisation est associee a quelque autre méthode de traitement elimination de l allergene, cure climatique et traitement symptomatique selon la necessite

Nous avons obtenu des resultats particulièrement satisfaisants avec la *cure climatique à la mer* (55 56) et dans des *localites d altitude* (57) Comme Turban et Spengler (58) Piery (59) Pasteur Vallery Radot (60) Blamoutier (63) nous avons aussi obtenu la cessation des crises des les premiers jours du sejour dans 70 p 100 des cas L action du traitement climatique est de plus longue durée si le sejour a ete prolongé s il est répete plusieurs annees de suite et si l asthme est plus recent Parfois cette action n est que temporaire Le fait que dans les localités de montagne les réactions allergiques soient rares meme quand les tests cutanes positifs sont frequents semblerait dire qu il existe dans le climat d altitude certains facteurs qui freinent les manifestations allergiques meme si toutes les conditions d allergisation sont presentes

L influence favorable du climat d altitude est attribuee a divers facteurs purete de l air et pauvrete en allergenes absence des causes de viciation de

l'air décompression (Harvat et Macoun) (62) changements dans le système endocrino végétatif (Wissler) (63) En Yougoslavie sauf en Slovenie nous n'avons pas de stations d altitude pour les enfants et les adultes asthmatiques mais on utilise à cet effet les chalets de montagne existant sur toutes les plus hautes montagnes

Les examens de l etat de l allergie chez les ouvriers de differentes fabriques chez les habitants de certaines agglomerations et de diverses régions de notre pays ont montre le grand role de *l assainissement* dans le traitement de l asthme Ainsi la construction d une digue le long du Danube il y a vingt cinq ans, grâce a laquelle les agglomerations des marecages de Pančevo ont ete asséchees a fait que le pourcentage d asthmatiques y est plus faible 0 9 p 100 alors qu il est en moyenne en Voivodina de 3 5 p 100 (64) La regularisation de quelques ruisseaux de la banlieue de l ancien Beograd et l installation des egouts dans ses rues ont abaisse le pourcentage d asthme au cours de vingt ans de 4 p 100 a 0 4 p 100 (65) Des etudes detaillees des rues asthmogènes de Beograd (67) ont fait ressortir l influence defavorable des rues étroites et fermees dans lesquelles l air pour ainsi dire ne circule pas ainsi que celle des conditions anti hygieniques des logements et des cours Sur le boulevard de la Revolution qui a 3 kilometres de long sur 40 metre de large a son extremite proche du centre de la ville et bien que plus basse mais ou il y a assez de parcs et des espaces verts et ou les appartements sont modernes et neufs il y a cinq fois moins d asthmatiques que dans la partie haute de ce boulevard plus elevee et dans la banlieue de la ville mais ou les conditions de logements ne ont pas aussi satisfaisantes L influence favorable des logements construits d apres les regles de l hygiene de l urbanisme moderne et de l hygiene communale est confirmee nettement aussi par d autres rues

Les pourcentages differents de manifestations allergiques dans les divers ateliers d une meme fabrique montrent clairement aussi l influence defavorable de certaines conditions de travail Bien que l allergene soit le meme que les conditions socio economiques soient plus ou moins les memes pour tous les ouvriers les conditions locales sont differentes (abondance de l allergène hautes temperatures évaporation des produits chimiques humidité etc) Cette influence des facteurs locaux est encore confirmee par la cessation des manifestations allergiques si ces conditions sont supprimees ou si les ouvriers passent dans d autres ateliers ou les conditions sont meilleures (67)

Nous voyons donc que le role de l assainissement est grand mais avant d entreprendre les mesures necessaires il faut etudier soigneusement toutes les conditions locales defavorables

INSTRUCTIONS ET ORGANISATION

En Yougoslavie il n existe pas encore de specialisation dans les maladies allergiques Cependant le rapide accroissement du nombre des allergies *exige que cette specialité soit réalisee le plus tôt possible* Ce sont les medecins specialistes d autres domaines de la medecine médecine dermato venérologie oto rhino laryngologie maladies professionnelles

chacun dans son domaine s occupent actuellement des maladies allergiques Le nombre de ces médecins est de 400 sur 11 000 en Yougoslavie

Dans les plus grands centres Beograb Zagreb Sarajevo des societes allergologiques locales existent (Section de la Societe des medecins serbes, Societes des medecins de Croatie Societes des medecins de Bosnie et d Herzegovine) *comprenant chacune de 20 a 100 membres et qui sont tres* actives La fondation d une société allergologique yougoslave est en voie de formation Dans les villes plus importantes dans lesquelles il n existe pas de société allergologique les problemes du domaine de l allergologie sont traites dans les societes des médecins de ces villes Ljubljana Novi Sad Split Niš Subotica etc Ces memes problemes sont egalement traités dans les symposia et les congres organisés frequemment dans le pays

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les Facultes de Medecine de Zagreb et de Ljubljana L enseignement pratique a lieu dans les cliniques et dans les services de medecine interne de dermato vénerologie d oto rhino laryngologie dans les instituts pour les *maladies professionnelles* et dans les ambulances de la Securité Sociale Il existe un precis sur les maladies allergiques (68)

A Beograd c est l Institut de recherches medicales de l Academie Serbe des Sciences qui s occupe surtout des problemes d'allergie En collaboration avec certaines cliniques et instituts pour la medecine du travail et l hygiene et souvent avec l aide materielle de la Commission pour les recherches medicales (Komnis) cet Institut a organi e de nombreux examens dans différentes fabriques et dans les regions les plus diverses du pays Les resultats de ces travaux sont communiques a l Academie Serbe des Sciences dans les symposia et congres en Yougoslavie et à l etranger A Zagreb a part la clinique dermato vénerologique que dirige depuis des annees l allergologiste renomme Franc Kogoj puis la Clinique oto rhino laryngologique l Institut pour l hygiene du travail de l Académie des Sciences de Yougoslavie s occupe aussi d allergie Les Academies Yougoslave et Serbe des Sciences ont publie chacune un symposium sur l allergie (69 70)

La population du pays est renseignee periodiquement sur les dangers presentes par les maladies allergiques, par des articles et des comptes rendus dans les journaux quotidiens par des conferences tenues dans les Universités populaires et ouvrieres par des émissions a la radio et par les examens faits par nos équipes dans un grand nombre de fabriques et d agglomerations et dans les regions les plus reculees du pays

CONCLUSION

L etude de l etat de l allergie en Yougoslavie a mis en évidence l importance des conditions locales en tant que facteurs essentiels d allergisation sensibilisation constitution du tissu de choc et hypersensibilité des effecteurs Ce sont ces conditions qui font qu en général l état de l allergie est si different suivant les milieux et les regions Nos examens montrent que meme si l assainissement par la suppression des conditions defavorables de travail et de vie influe sur la diminution des manifestations allergiques

bientot la civilisation elle meme deviendra l une des causes les plus importantes de l accroissement du nombre des maladies allergiques La vie moderne avec sa constante augmentation des allergenes la viciation de l air toujours plus grande le système nerveux sans cesse exposé à des « stress » tout cela réuni a une résistance de plus en plus faible et à l endurcissement des individus amène une augmentation continuelle des manifestations allergiques Au contraire la rareté de ces manifestations dans les regions montagneuses ou la vie est simple naturelle équilibrée et saine indique que dans la lutte contre les maladies allergiques il faut s inspirer aussi de ces faits Du reste cette tendance se manifeste de plus en plus dans beau coup de pays civilisés

RÉSUMÉ

En Yougoslavie et surtout dans la R P de Serbie donc sur une étendue relativement faible on peut voir nettement l influence des conditions locales sur l apparition des manifestations allergiques Par suite des conditions climatiques géographiques socio économiques differentes de l industria lisation de la longue influence de civilisations diverses et d autres encore les maladies allergiques se manifestent tout a fait différemment suivant les régions de Yougoslavie La région la plus defavorable est la Voivodina avec de 3 a 5 p 100 d asthmatiques et 23 p 100 d allergies en général La Voivo dina est une plaine basse (82 86 m d altitude) inondable et fertile faisant partie de la plaine pannonienne Dans cette region soumise pendant des sie cles à l influence de la civilisation occidentale l agriculture et l industrie sont très développées L alimentation de la population est tres bonne Au contraire dans les regions montagneuses de la Serbie meridionale (1 000 2 500 m d altitude) il n y a que 0 4 p 100 d asthmatiques et 3 p 100 d autres allergies Dans ces régions d élevage plus pauvres ou la majorite des habitants menent encore une vie patriarcale et dont l alimentation est principalement constituée de laitage et de végétaux avec de la viande seulement de temps en temps et surtout en hiver les hommes sont maigres élancés vigoureux et résistants

Ces conditions differentes suivant les régions changent aussi le role meme de la plupart des facteurs d allergisation infection conditions d hygiene des habitations industrialisation et civilisation Ce qui saute aux yeux c est que parmi la population rurale il y a peu de sensibilises au pollen et peu de rhumes des foins comme aussi peu de sensibilisés aux poils d animaux chez les habitants des régions d élevage

En Yougoslavie a part les methodes thérapeutiques habituelles desen sibilisation spécifique medicaments antihistaminiques thérapie hormonale des resultats particulierement favorables ont été obtenus grâce à l assainis sement aussi bien des ateliers des conditions logement que de régions entieres (assechement des terrains regularisation des rivières installation des égouts constructions de nouveaux logements hygiéniques etc)

Cependant dans les regions industrielles du nord du pays ou la civilisation est plus avancée il est apparent que c est justement cette civilisation qui

influe défavorablement sur l apparition des manifestations allergiques La vie moderne a une influence sur l accroissement des allergies avant tout par l augmentation constante des allergenes (médicaments produits cos métiques produits divers ajoutés aux vivres ou conserves alimentaires afin d améliorer leur gout leur couleur leur aspect leur conservation etc) ensuite par viciation de plus en plus forte de l air surtout dans les grands centres industriels par la tension perpetuelle du systeme nerveux et les continuels « stress » Au contraire la rarete de ces manifestations dans les regions montagneuses ou la vie est simple naturelle équilibrée et saine indique que dans la lutte contre les allergies il faut s'inspirer aussi de ces faits Du reste cette tendance se manifeste de plus en plus dans beaucoup de pays civilisés

SUMMARY

In Yugo Slavia chiefly in the Serbian Republic which means a limited area the incidence of allergic diseases on local life are perceivable

On account of the climate geographical location social and economical differences the long lasting influence of various civilizations of industria lization and of many other factors allergic diseases appear under different forms according to the parts of the country where they occur The less favoured part of the country is the Voivodina with 3 p 100 to 5 p 100 of asthmatic subjects and 23 p 100 of allergic diseases in general

The Voivodina is a low lying flat country (82 to 86 meters above the sea level) often flooded and fertile belonging to the Pannonian plain In this country which has been for many centuries submitted to western civili zation agriculture and industry are well developped The population enjoys very good food conditions

In the moutainous areas of Southern Serbia (altitude 1 500 to 2 500 m) we only find rates of 0 4 p 100 for asthma and 3 p 100 for other allergic diseases In this cattle breeding country and poorer country most inhabi tants still lead a patriarchal life, the food is light and based on milk and vegetables meat is only occasionally eaten and chiefly during the winter men are lean slender, strong and hardy

Different living conditions in various parts of the country have their incidence on allergic factors infections house hygiene, industrialization degree of civilization a s o

Striking facts are that sensitization to pollens is rare among the rural population hay fever is uncommon and rare sentisization to animal s hairs in the cattle breeding districts

Usual therapy is employed specific desensitization anti histaminic remedies hormonal treatments and besides good results have been obtained by the applying of general welfare measures such as improvement of living conditions, workshops and houses and whole districts (draining of marshy land regularizing of rivers building of new and healthy houses sewers a s o)

Yet in industrial areas of the North of the country where civilization has reached a high standard it seems that this very civilization favours the development of allergic diseases

Modern life exerts it s influence on the increasing number of allergens

(remedies cosmetics various substances added to canned foods to improve their taste their colour their appearance and their preservation a s o)

The increasing impurity of the air chiefly in industrial districts also plays an important part as well as the increasing nervous strain and permanent stress

To the opposite in mountainous countries where life is simple natural steady and healthy allergic diseases are rare

During our fight against allergic diseases these facts must be born in mind moreover this tendancy nowadays comes to light in many civilized countries

ZUSAMMENFASSUNG

In Jugoslavien besonders in der serbischen Republik als abgegrenzten Landstrich ist der Einfluss allergischer Krankheiten auf das lokale Leben deutlich wahrzunehmen

Wegen des Klimas geographischen Lage sozialen und okonomischen Unterschiede den bestandigen Einfluss verschiedener Zivilisationen der Industrialisierung und wegen verschiedenen anderen Faktoren treten allergische Erkrankungen unter verschiedenen Formen auf betreffend den verschiedenen Landstrichen Der ungunstigste Teil des Landes ist die Voivodina mit 3 5 p 100 Asthmatikern und 23 p 100 allergischen Erkrankungen im allgemeinen

Die Voivodina ist ein tiefliegendes flaches Land (82 bis 86 m uber den *Meeresspiegel) oft uberflutet und fruchtbar das zur pannonischen* Ebene gehort In diesem schon einige Jahrhunderte der westlichen Zivilisation zugehorenden Land ist Ackerbau und Industrie gut entwickelt Die Bevolkerung ist sehr gut ernahrt

In den gebirgigen Regionen von Sudserbien (Hohe 1 500 bis 2 500 m) *finden wir nur Zahlen wie 0 4 p 100 fur Asthma und 3 p 100 fur andere* allergische Erkrankungen In diesem armeren die Viehzucht betreibenden Land fuhren die meisten Einwohner noch ein patriachalisches Leben die Nahrung ist leicht und besteht aus Milch und Vegetalien Fleisch wird nur selten gegessen und besonders wahrend des Winters die Leute sind *schlank mager kraftig* und abgehartet

Unterschiedliche Lebensbedingungen in den verschiedlichen Teilen des Landes beeinflussen die allergischen Faktoren Infektionen Haushygiene Industrialisierung Zivilisationsgrad usw

Auffallend ist dass eine Pollensensibilisierung bei der landlichen Bevolkerung selten und Heufieber unbekannt ist eine Empfindlichkeit Tierhaaren gegenuber in Viehzucht betreibenden Landstrichen ist auch selten

Die ubliche Therapie wird angewandt spezifische Desensibilisierung *Antihistamingaben hormonelle* Behandlung *un daneben konnten gute* Resultate mit allgemeinen Wohlfahrtsmassnahmen erreicht werden Verbesserung der Lebensbedingungen Werkstatten Hauser und ganzer Distrikte (Drainage von sumpfigem Gelande Flussregulierungen Bauen von neuen und gesunden Hausern Kanalbau usw)

Im industrialisierten Norden des Landes wo die Zivilisation einen hohen Standard erreicht hat scheint diese Zivilisation das Auftreten von allergischen Erkrankungen zu fordern

Das moderne Leben ubt seinen Einfluss in einer zunehmenden Zahl von Allergenen (Medikamente Kosmetika verschiedene Substanzen die konservierten Nahrungsmitteln zugesetzt werden um den Geschmack die Farbe das Aussehen zu erhalten und eine lange Aufbewahrungsdauer zu gewahrleisten usw)

Die zunehmende Luftverunreinigung besonders in Industriegegenden spielt auch eine wichtige Rolle

Im Gegensatz dazu sind allergische Krankheiten in gebirgigen Gebieten selten wo das Leben einfach naturlich solid und gesund ist

Wahrend unseres Kampfes gegen die allergischen Krankheiten mus man sich dieser Faktoren erinnern uberdies tritt diese Tendenz in vielen zivilisierten Landern zu Tage

RESUMEN

En Yugoeslavia y sobretodo en la R P de Serbia es decir en una extensión relativamente pequena puede verse netamente la influencia de las condiciones locales sobre la aparición de las manifestaciones alergicas Como consecuencia de las condiciones climáticas, geográficas económico-sociales industriales de civilizaciones diversas y otras las enfermedades alergicas se manifiestan diferentemente segun las regiones del país La zona más desfavorable es la Voivodina donde hay 3 a 5 p 100 de asmaticos y 23 p 100 de alergicos en general La Voivodina es una llanura baja (82 a 86 m) inundable y fértil que forma parte de la llanura panoniana En esta región que ha estado durante siglos bajo la influencia de la civilización occidental están muy desarrolladas la agricultura y la industria La alimentacion de la población es muy buena Por el contrario en las regiones montañosas de la Serbia meridional (1 000 a 2 500 m) no hay sino 0 4 p 100 de asmáticos y 3 p 100 de alérgicos En estas regiones donde especialmente se cría ganado más pobre los habitantes llevan todavia una vida patriarcal y se alimentan a base de leche y vegetales comiendo carne sólo de tanto en tanto y en invierno La gente es delgada alta vigorosa y resistente

De esta manera las mismas condiciones de vida diferentes de una a otra region cambian la importancia de los factores alergizantes infecciones higiene de la vivienda industrialización y civilización Lo que es evidente es que hay pocos sensibilizados al polen en la población rural y tambien poca frecuencia de rinitis debidas a pelos de animales entre la poblacion de las zonas ganaderas

Aparte de las medidas terapeuticas usuales en Yugoeslavia se han obtenido resultados especialmente favorables mediante el saneamiento de fabricas viviendas y aun regiones enteras (desecación de terrenos canalización de rios construcción de cloacas construcción de viviendas higiénicas etc) Sin embargo dirfase que en las regiones más civilizadas del país es justamente esa civilización la que crea condiciones favorables para la aparición de las enfermedades alérgicas La vida moderna tiene una influencia sobre el aumento de las alergopatías debido a la mayor cantidad de alergenos que supone (medicamentos cosmeticos condimentos colorantes conservadores etc) al enviciamiento de la atmósfera sobre todo en los grandes centros industriales a la constante tensión nerviosa Al contrario la rareza

de estas manifestaciones en las regiones montañosas donde la vida es simple natural equilibrada y sana indica que en la lucha contra las enfermedades alérgicas no deben olvidarse estas circunstancias Por otra parte se trata de tendencias observadas en muchos otros países civilizados

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NETHERLANDS

by

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Holland a small country on the North Sea with its long coast line consisting of a broad beach and dunes behind which there is a strip of meadows farm lands and bulb fields with sandy moors heath and forests further east Holland which has a comparatively mild climate marked by unsteady weather in summer and mild winter weather a relatively large amount of rainfall and little sun with a population of 11 000 000 living on an area of 32 405 59 square kilometres Amsterdam being the only town characterized by the atmosphere typical of large cities a country with considerable agriculture and industry nevertheless is familiar with all the problems of allergic disease to the solution of which such early investigators as Storm van Leeuwen and Kremer devoted their energies

The subject on which the largest number of data are available is the incidence of allergy (1)

One conducting an inquiry in the north obtained the following results 0 59 p 100 asthmatic patients on a material of 40 000

Doeleman elaborated an investigation carried out by school medical officers among schoolchildren and obtained the following results 3414 of 269 015 children suffered or had suffered of asthma (1 2 p 100)

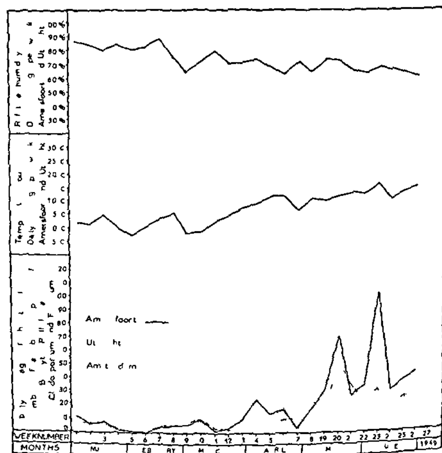
The present author elaborated the data obtained in medical examinations for enlistment the proportion of cases of bronchial asthma being found to be 0 933 p 100 in a number of 171 737 conscripts

All forms of bronchial asthma were reported asthma following contact with all sorts of pollen asthma due to fungi asthma caused by house dust attacks of asthma following and during bronchitis emotional asthma asthma like attacks due to pulmonary lesions as well as a wide variety of allergens and mixed forms of asthma

Vasomotor rhinitis due to contact with fungi dust bed fillings flowers foods etc etc hay fever from February (when catkins are flowering) to October (first night frost) from April to October from the end of May to

the middle of July (grasses) from May to September in August urticaria angioneurotic oedema ring worm, allergic eczema and contact eczema all these conditions are frequently observed and studied

The exact incidence of these conditions is unknown Franssen (2) report



GRAPH 1 —a) Annual review of the weekly average daily incidence of the spores of so called seasonal fungi collected at the same time in 3 different places in the Netherlands and the temperature and relative humidity of the outdoor atmosphere in the Central Netherlands

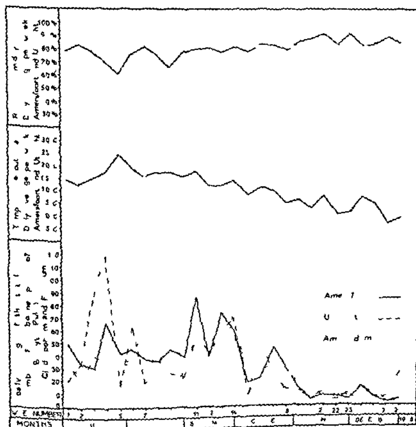
P J VAN DER WERFF *Mould Fungi and bronchial asthma* Leiden 1958

ed a nasal f... d out among students found on ± 524 stu

Personal studies were done among nurses of medical services in sanatoriums and hospitals distributed throughout the Netherlands The results obtained are shown in the graphs 1

Like the climate the various allergic diseases also are average in type There is no form of allergic disease known to be especially or mainly common in the Netherlands

Unfortunately, it is difficult to decide whether and in what proportion of cases allergic reactions tend to occur in typically Dutch trades and industries One of our poets said thinking of Holland I see broad rivers moving slowly through interminable lowland rows of countless poplars appearing



GRAPH 1 — b) Annual review of the weekly average daily incidence of the spores of so called seasonal fungi collected at th same time in 3 different places in the Netherlands and the temperature and relative humidity of the outdoor atmosphere in the Central N therlands

P J VAN DER WERFF *Mould Fungi and bronchial asthma* Leiden 1958

mould like on the horizon Meadows fields of waving corn cattle (though horses are disappearing from the country and the towns) these are found all over the world

The clog making industry does not involve any problems the bulbgrowing industry is well known apparently bulb eczema is fairly common however as it only occurs during the short bulb cleaning period (July ... hyacinths workers usually attach little impor

chitis are very apt to occur, ...
ing to the official data subm . . . . .
Association allergic reactior . .
very preliminary survey of an investigation recently carried out in a cigar factory offers no foundation for this optimistic statement cases of dermatitis and dyspnoea have been known to occur in this industry cases of bronchial asthma due to hypersensitiveness to fungi growing on tomatoes are known to occur in the tomato growing industry, cases of bronchial asthma vasomotor rhinitis and dermatitis are fairly common in flower nurseries (chrysanthemums have acquired particular notoriety as a cause of these conditions) little is known concerning the gin industry (distilling of gin)

Six of the largest gin distilleries were asked whether sensitivity reactions had been known to occur during distillation

Curiously enough the reply was that the management was not aware of any reactions in distilleries where alcohol was the material used in making gin Several managers even expressed the opinion that the handling of alcoholic agents has a disinfectant action

Likewise few if any reactions are claimed to occur in liqueur factories where workers handle herbs rinds peel etc

When flour is used for manufacturing purposes instead of alcohol matters become entirely different

One of the largest distilleries has two departments viz a malt and milling house and a distilling department Flour from maize rye and malting barley is used in both departments

Sensitivity reactions consisting in fits of sneezing asthmatic attacks and febrile symptoms occurring at night are observed in certain employees of this company Their condition was sufficiently severe to warrant a change of employment in a few cases only

Extensive investigations were carried out on the allergens most dreaded in the Netherlands

POLLENS in the land of willows and alders of fir and lime trees of many kinds of fl . . . and in wide
lle of Octo-
ides a plant
chart and an extensive list of grasses, plants and trees which may act as allergens as well as their flowering seasons

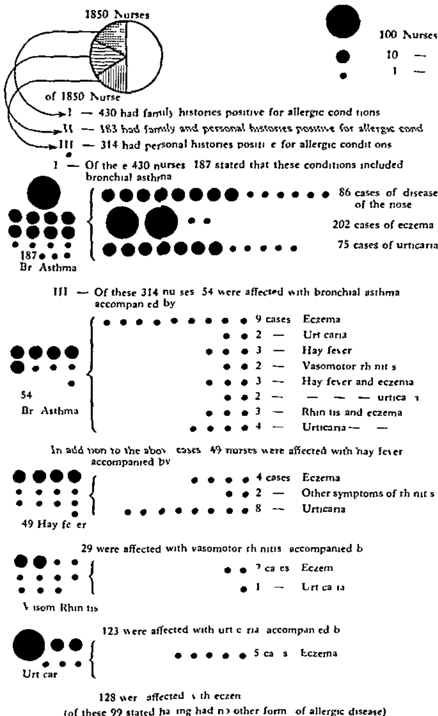
FUNGI Orie did a detailed study on spores van der Werff studied fungi (graph 2) in conjuction with Professor Johanna Westerdijk

The latter author (4) stressed the fact that the most common fungus is not always the most important allergen and that an extensive knowledge of the various culture media required is essential in the isolation and cultivation of fungi

Two seasonal peak incidences of asthma are attributed to fungi, that during the period from February to March and that during the period from the middle of August to the middle of October

ANIMALS When cattle are put in the stall this causes attacks of asthma in a number of farm house occupants In addition there is the condition known as milkers eczema

Besides cats and dogs, canaries (and canary seed) are frequently found to



1850 Nurses
100 Nurses
10 —
1 —
of 1850 Nurse
I — 430 had family histories positive for allergic conditions
II — 183 had family and personal histories positive for allergic cond
III — 314 had personal histories positive for allergic conditions
I — Of these 430 nurses 187 stated that these conditions included bronchial asthma
86 cases of disease of the nose
202 cases of eczema
75 cases of urticaria
187 Br Asthma
III — Of these 314 nurses 54 were affected with bronchial asthma accompanied by
9 cases Eczema
2 — Urticaria
3 — Hay fever
2 — Vasomotor rhinitis
3 — Hay fever and eczema
2 — — — — urticaria
3 — Rhinitis and eczema
4 — Urticaria — —
54 Br Asthma
In addition to the above cases 49 nurses were affected with hay fever accompanied by
4 cases Eczema
2 — Other symptoms of rhinitis
8 — Urticaria
49 Hay fever
29 were affected with vasomotor rhinitis accompanied by
2 cases Eczema
1 — Urticaria
Vasom Rhinitis
123 were affected with urticaria accompanied by
5 cases Eczema
Urticar
128 were affected with eczema
(of these 99 stated having had no other form of allergic disease)

GRAPH 2

give rise to vasomotor rhinitis An old superstition carries the pigeon into the bedrooms of patients with allergic eczema the pigeon is assumed to draw the eczema away from the patient and towards itself

HOUSE DUST this is the most common allergen studied in detail by Storm van Leeuwen (5) Skin tests were found to be positive in 83 7 p 100 of 1 000 cases in asthmatic patients and in 76 p 100 of 200 cases of vasomotor rhinitis (6) House dust frequently causes sneezing or dyspnœa on awaking at home in the evenings during week ends on days off spent at home during the spring cleaning season which has acquired such notoriety in Holland in the early part of spring and in autumn when life indoors is again becoming increasingly active

BED FILLINGS mattresses pillows and eider downs filled with Alpine grass sea weed straw feathers or kapok play an important part in our lives Hypersensitiveness to feathers is fairly common pure hypersensitiveness to kapok is fairly rare though hypersensitiveness to kapok which has undergone [illegible] and those using

FOOD when an allergic origin is suspected in cases of asthma rhinitis urticaria strophulus or eczema occurring in the Netherlands and food may be the offending substance the patient is usually placed on a standard elimination diet in which chocolate, fish pork eggs spinach endive tomatoes and if need be milk and pulses are prohibited Kremer believed food allergy to be of considerable importance and therefore there even was an industry which marketed food extracts for use in intradermal tests and supervised by Kremer

CONTACT ALLERGENS bakers itch and brick layers itch are particularly common (graph 3) The work done by Mali and Malten in the field of social welfare has been of great importance with regard to these forms of disease as the Government Insurance Bank regards only a few types of occupational eczema as coming within the scope of the workmen s compensation act Detailed histological studies and accurate examination of the constituents of substances handled by the workers showed that the view according to which only a few substances were recognized as the causative agents in eczema within the meaning of the workmen s compensation act was no longer tenable

INFECTIONS when their histories are taken many patients with asthma and rhinitis state that they feel much better in a winter marked by hard frost than they do in winters during which the weather is unsteady Influenza and bronchitis also are much more common in mild winters The time of onset of a large number of asthmatic attacks, both those occuring for the first time and recurrent attacks probably is the period following about of influenza or bronchitis In addition symptoms of bronchitis often appear as complications Mulder (8) who did extensive studies on the subject drew particular attention to *Hæmophilus influenzæ* as a highly important factor in infections of the bronchi In addition to courses of antibiotics and general measures designed to increase resistance autovaccines and standard vaccines are also used in a large number of cases with a view to treating both the primary and the secondary complicating bronchitis in order to prevent subsequent attacks of bronchitis Other sites of bacterial infection (ton

sils nasal sinuses gall bladder etc) are treated with autovaccines as well as courses of antibiotics and surgical procedures

When the dosage is carefully determined, responses being closely super vised fresh vaccines prepared several times if necessary and sufficient patience exercised extremely favourable results may frequently be obtai ned

When a clash occurred between two theories on the interrelationship bet

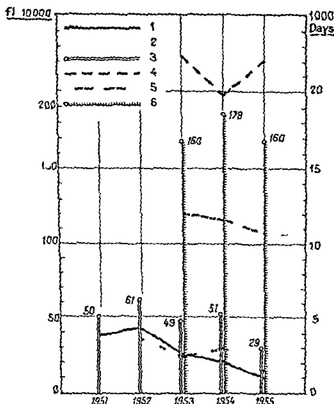


Fig 3 — Since only in the course of 195 was decid d that cement eczema has to be considered as an occupational d sease a cording to the accident insurance law of 1921 the records of this occupational disease a e limited to the years of 1953 till 1955 included

Moreover the remark has to be made that as net charges are to be considered all payments consequently as well those al eady effected as those that have still to be effected

The administrat on costs are not included in these amounts

1 paid amount of money because of bakers eczema
2 lost days of wo k because of bakers eczema
3 number of cases with bakers eczema
4 paid amount of money because of cement eczema (in 10 000 gu lders)
5 lost days of work (n 1 000 days)
6 number of cases with cement eczema

ween sinusitis and bronchiectasis, that of infection haute on the one hand and that of infection basse on the other, this give rise to an interesting

patient as well as detailed histories The patient is extensively examined Stories claiming that tuberculosis passed unnoticed in a patient with bronchitis whereas his begonia allergy was detected and treated, and that the case in which treatment by an allergist was most successful was that in which he prohibited the use of meat to a strict vegetarian following skin tests have no foundation in actual fact

Physical examination laboratory tests X raying with a view to studying the general condition of the patient examination for complicating diseases or focal infections if any frequently are preliminaries to actual testing for allergy Scratch tests prick tests and intradermal tests are all made As a rule from 60 to 80 routine extracts of inhalant and food allergens are used in the initial examination as well as extracts prepared in view of the history In determining the concentration of the extracts it is usually assumed that the latter should not elicit reactions in normal subjects the response elicited in an individual known to be hypersensitive to this extract being marked though not too intense

As a rule the extracts are prepared in accordance with Coca s specifications the method adopted by Maunsell (boiling in a water bath for 30 minutes on three consecutive days) being found to be very useful in preparing extracts of various inhalants Van der Werff stressed the fact that the choice of a correct culture medium (varying with the different fungi) and utilization of the fungi at the correct stage of growth are essential in preparing fungus extracts Except when testing for bacteria little value is attached to skin tests of the delayed type

Besides skin tests inhalation provocation tests (Orie ten Cate) (10) are also used in examining patients for respiratory allergy the Prausnitz

are mainly used in urticaria in which skin testing for allergens often fails

The patch test is particularly useful in testing for contact eczema

Studies showed nephelometry (Cormane) (11) to be of doubtful value It continues to be difficult to convince the majority of physicians of the value of making a skin test prior to starting another treatment with antiserum or antibiotics The Utrecht school of van Hoogenhuyze Julius Hamburger and Winkler attached considerable importance to detailed examination of the sputum as well as examination for focal infection and treatment with autovaccines In a number of cases the vaccine is prepared on the basis of strongly positive bacterial tests Binkhorst and Quarles van Ufford (12) made extensive tests for allergy in patients with chronic uveitis the main findings being strongly positive skin tests for bacteria

In addition to testing for possible foci complications and causative allergens considerable value is attached to the answer to the question as to whether a patient may be defined as allergic family history of allergy personal

history of allergic disease examination of the blood, sputum, nose, etc for eosinophils (Franssen Voorhorst Savelberg) (13) and other symptoms regarded as allergic such as hypotension low blood glucose levels diminished or increased basal metabolism low stomach acid levels low adrenal function tests changes in the chemical composition of the blood occasional changes in the electroencephalogram etc etc These tests as well as examination by a psychiatrist and investigations carried out by welfare workers are extremely valuable diagnostic aids in difficult cases

Detailed studies on clinical cases by the team of investigators of the Diaconessenhuis Utrecht engaged in the study of asthma (including an allergist who introduced the patients to a pediatrician a cardiologist a chest physician a roentgenologist an otologist 3 psychiatrists and a welfare worker) brought home the fact that a consideration of the entire background is essential in treating these patients in whom several factors are often mixed up together patients with true allergy like those with genuine nervous asthma or having a true psychosomatic constitution are relatively uncommon in this group (14)

Vossenaar and Quarles van Ufford (15) did extensive histopathological studies on the lesions of urticaria which revealed marked differences between the wheals due to allergic urticaria and those observed in positive skin tests on the one hand and the lesions observed in congelation urticaria and factitious urticaria (dermographism) on the other The cellular infiltration which is an outstanding feature in the former group, was always found to be entirely or almost entirely absent in the latter group

TREATMENT — Treatment with antihistaminics (graph 4) often conti-

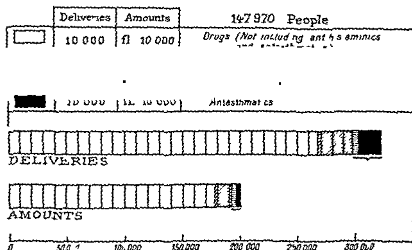


FIG 4

nued over prolonged periods and grass pollen desensitization therapy (5 proprietary pollen extracts for use in complete courses of treatment are readily available) are much in vogue so that these methods are even used in the treatment of other patients with vasomotor rhinitis showing symptoms

of hay fever and therefore labelled accordingly *Preventive treatment* is given from January to May when treatment is discontinued by some practitioners whereas others continue administering a maintenance dose during the hay fever season, perennial treatment having found little acceptance to date Results usually are satisfactory in patients subjected to a detailed preliminary examination There are difficulties in treating certain patients as they continue to respond by severe attacks of urticaria or asthma even when small doses are administered The methods adopted in these cases are preliminary treatment with antihistaminics, A C T H protection or injections into the skin which has been previously cooled with ice

Naturally allergists also frequently use courses of treatment with house dust extracts fungus extracts extracts of flowers and pollen occasional extracts of human and animal hair, and extracts of bed fillings some allergists using autovaccines administered percutaneously and subcutaneously Histamine and staphylococcus toxoid are widely used in the treatment of patients with dermatitis The scheme of dosage varies to some extent initially injections are made three times weekly the dose and the interval between injections then being gradually increased the ultimate dosage consisting in one injection made at monthly intervals The extract is administered subcutaneously or intradermally larger doses being given partly intradermally and partly subcutaneously

Treatment is continued over prolonged periods patients with hay fever being treated for years on end, while fungus and dust extracts are also administered for periods of several years

Oral desensitization is occasionally carried out in severe cases of food and drug allergy (*e g* eggs milk aspirin) the result being that any contact with [illegible] hich [illegible] ls of *cortisone* A C T H given intramuscularly and by intravenous drip (the choice of drug was often found to be an important factor, as well as the animal (swine cow) from which it was prepared), preparations of penicillin having a delayed action and courses of prednisolon are mainly used in the severe acute stage

These drugs are also used in a number of carefully selected chronic cases which anyway are in danger of disability On the whole practitioners continue to be hesitant about using these agents in infants and young children An expectant attitude is usually adopted in these cases

An important finding was that reported by van Geuns (16) and verified by others who detected a large number of eosinophils in the sputum in a number of cases of tuberculosis showing little if any improvement treatment with multergan (in which the atropine like side effect also was beneficial) occasionally produced a striking improvement in these cases

There are no spas and mountains in the Netherlands but moving from a large town to the heath or seaside from a humid river district to dry sandy soil from the seaside to the heath or vice versa occasionally had a beneficial effect, especially in cases of rhinitis and bronchial asthma

The out patient and clinical departments of the 7 allergists (to about 2 150 licensed specialists and about 4 200 family practitioners) are available for treatment and those specializing in other branches of medicine

sometimes are also interested in certain forms of allergic disease dermatologists widely experienced in the field of allergology are interested in allergic dermatitis Professor van Dishoeck s students being mainly concerned with allergic diseases of the nose

Increasing general interest is being taken in bronchial asthma Initially activities in this field were confined to Professor Orie s hospital in Groningen (the work done by Groen as well as that of Stokvis and Welman in the field of psychosomatic medicine deserves special mention) but the declining incidence of tuberculosis has resulted in the use of sanatoriums for other purposes such as the treatment of asthma Large numbers of patients are examined in De Klokkenberg inhalation tests being mainly used in these cases whereas the Komingin Emmakliniek is especially concerned with the treatment of chronic patients the methods used in this hospital (e g densitization etc) also including treatment in activity groups occupational therapy sociotherapy vigorous psychotherapy and relaxation therapy

Centres for asthmatic children such as Heideheuvel and Willemijntje starting as centres enabling a change of environment and developing into complete hospitals for asthmatic patients with a large staff of consulting specialists have proved their usefulness over a period of several years

Several of those interested have joined the Dutch Society of Allergy established by van Dishoeck and Kremer in 1948 Kremer being the first chairman of the society The society has a membership of 80 it meets twice annually and sometimes a third meeting on a special subject was convened

Three meetings resulted in the publication of a booklet by the Stenfert Kroese Publishing Company Antihistaminics Mind and allergy and Hay fever

A fourth booklet The histopathology of allergic disease is in the press As scientific societies also have to look after the social interests of their members the founders and allergists are united in a special allergy group which protects the interests of allergists To be admitted as a member of this allergy gro[illegible]
spe[illegible]
mit[illegible]
laying down training requirements supervising training courses and registering specialists

Since September last requirements for training as an allergist are as follows

period of training 5 years viz

a) a three years course in internal medicine in an A hospital (the instructor may order that the first year be spent somewhere else (laboratory of physiology serology fungus or sputum research)

b) one year to be spent in an A hospital for children s diseases skin diseases diseases of the ear nose and throat a psychiatric establishment or an institute of medical psychology as desired

c) one year to be spent in a department of allergology (hospital out patient department)

To be recognized as an allergology instructor certain requirements relating to character teaching abilities library scientific interests the organiza

tion of evenings in which papers are read a sufficient number of patients and opportunities for hospitalization have to be complied with

The Society has set up two committees To begin with there is the Drugs Committee for allergic disease which promotes research (such as the current studies on recent views regarding the local action of antihistaminics on the skin and investigations on a generally effective indifferent ointment base)

Another committee is the Standardization of Vaccines and Extracts Committee This committee organized a day of study on the subject This has had the useful effect that since then the expiration date has been accurately stated on several extracts marketed in the Netherlands

One of the allergists also is on the staff of a university the Leyden University Hospital for Diseases of the Ear Nose and Throat has a department of allergy where a considerable amount of research is being done under the direction of Professor van Dishoeck a specialist in diseases of the ear nose and throat and R Voorhorst an allergist

Further university training as an allergist is provided for by the other departments of medicine Lectures on immunology involve a detailed theoretical discussion of allergology, during the years of hospital training classes are held in hospitals for internal medicine as well as hospitals for diseases of the lungs skin diseases and diseases of the ear nose and throat

Allergists are frequently invited to read papers at medical classes and local meetings of the Society

Though the teaching of allergy to students is merely in its infancy public interest has developed to a far greater extent Since the shafts of Storm van Leeuwen s allergen free chamber have been pointing up high into the air people have become accustomed to terms such as cat asthma feather asthma hay fever chocolate urticaria etc etc The psychosomatic school of medicine however has set its mark on the attitude adopted towards these conditions Allergic eczema is often called nervous eczema and bronchial asthma is referred to as nervous asthma people have come to realize the fact that mortality from tuberculosis is constantly declining whereas that from bronchial asthma is increasing (graph 5) Moreover in the more and more ordered society of to day people are constantly being confronted with the problem of chronic disease

The mere statement that an applicant has a history of bronchial asthma is sufficient reason for a large number of industries to reject him for fear of absenteeism or excessive disability and other pension benefits

Examination for enlistment often the first medical examination to be undergone by the young men also frequently causes disappointments The Inspector of the Army Medical Corps (Land and Air Forces) kindly supplied the following data Individuals having mild attacks of asthma at irregular intervals for instance during the flowering season of certain plants on eating certain foods etc may not be classified higher than A3 All those showing more severe forms of asthma corroborated by reliable certificates and the detection of pronounced symptoms (rhonchi, eosinophilia low and not freely movable lung borders) are classified as A5 and rejected as unfit for military service

Vasomotor rhinitis need not necessarily be a reason for classifying a man lower than A1 in the more severe cases the men will be classified as A2 or A3

Individuals affected with mild hay fever or having occasional severe attacks may be classified as A1. A pronounced and reliable history of mild hay fever will result in classification as A2. In the event of severe hay fever individuals are classified as A3.

Subjects affected with atopic dermatitis will usually be classified lower than

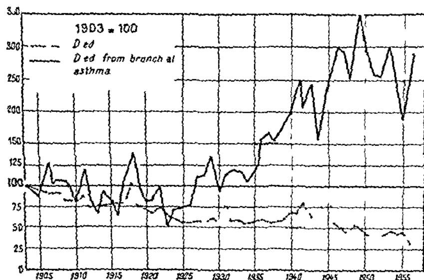


FIG. 5. — Asthma deaths

The low(e) figures for 1955 may be explain d by the f ct that an inquiry into the incidences of asthma during that year was held by the medical officer of the Central Bureau of Statistics. The replies received enabled a sharp r d ff rentiation between (allergic) bronchial asthma asthmat form chronic bronchitis and (solely) psychogen c asthma. As result bronchial asthma was l common as a cause of death during 1955 on the other hand chron c bronchitis as a caus of death and to a lesser extend the group of psychoneurotic somat c diseases were rather more common.

A1 the severity and extent of the lesions will decide whether they are to be rejected as unfit (A5) or classified as A_ or A3.

Those classified as A1 may be assigned to duty with all arms and branches of the service.

Those classed with lower categories are assigned to lighter duties thus those classified as A3 are only assigned to administrative technical or administrative and technical duties.

During their term of military service soldiers classed with too high categories at the initial medical examination and therefore assigned to duties for which their condition renders them unfit or not well suited may be classified again or rejected as unfit for military service. If they are not turned down as unfit but merely placed in a lower category (A2 or A3) new training recommendations (duty) may be made.

As a rule this occurs as the re examination made during basic training (so-called Tilanus examination) 6 weeks after joining up. However these

soldiers may even be classified again at a later date and, if necessary assigned to other duties in which their condition will cause little if any trouble

The rules followed in the Royal Navy are virtually identical

(1) Individuals with allergic disease usually are not passed fit for military service with the proviso that the history is a vital factor in forming an opinion on these cases

(2) When allergic conditions become apparent in individuals on military duty any rejections as unfit will be judged from one case to another and made dependent upon a variety of factors such as being suited or not suited for particular duties or for serving in a ship, being sent to the tropics stationing in a particular type of ship in connection with the branch of service etc etc

(3) Conscripts of the group referred to under (2) usually will be more readily rejected as unfit than professional soldiers

The difficulties involved in this type of medical examination are apparent from the standards imposed by one of the largest companies in the Netherlands the Netherlands Railway Company who require that a railway worker employed in the safety department shall be able to cope with the specific requirements of a difficult field of duty

Accordingly applicants for these posts will have to show several positive qualities only stable, sthenic well adjusted individuals in good health and having a large tension arc being eligible

Experience has shown that individuals predisposed to asthma or having a history of similar conditions who have been passed fit frequently meet with great difficulties in this sphere of work as soon as their condition becomes apparent which nearly always is the case These are persons who are difficult to employ and very difficult to re employ on re examination

In addition there is the fact that disturbances of consciousness and impairment of the power of concentration resulting from their condition (fits of coughing and black outs due to disturbances of the circulation in the brain) or from treatment (frequently consisting in the administration of sedatives hypnotics or both or ephedrine like drugs having side effects characteristic of stimulator amines) cannot be tolerated in the safety department of the company

Therefore passing these individuals as medically fit is not justifiable Requirements also have to be strict in the case of applicants for posts other than those in the safety department as the large number of those rejected as unfit for employment in the safety department will have to be assigned to non hazardous duties Accordingly these posts cannot be filled by partially disabled members of society

The rigid organization of society creates an urgent need for safeguarding against contingencies taking out sickness insurance policies for examination and treatment in out patient departments examination and treatment in a hospital, several times if need be admission to a centre for asthmatic patients over prolonged periods in the event of social or medical indications benefits on account of loss of income during sickness and finally having a proper life insurance

There has been marked improvement in this regard Formerly the presence of bronchial asthma was a reason for excluding all diseases of the

respiratory tract from a sickness insurance whereas to day policies can frequently be taken out against all forms of disease if at a slightly higher premium In the past the company was entitled to discontinue an insurance once a benefit had been paid to day the policy usually contains a clause stating that the company cannot cancel the insurance on account of benefits

Insurance against admission to so called centres is being contemplated A lot of work will yet have to be done until conditions can be called ideal but there is no mistaking the improvement obtained The problem of life insurance is rather more complicated as life insurance companies do not take a similar attitude in regard to this matter but frequently adopt widely different views which may even result in competition In a case of bronchial asthma one company may take the view that a life policy can only be taken out at a much higher premium whereas another will arrange an ordinary insurance without hesitation With the exception of very severe cases of emphysema certain companies are prepared to enter into an ordinary contract of insurance provided the policy is taken out up to the 60th year of life Matters then become difficult when a policy up to the 65th year of life is desired However the increasing interest in the life insurance business is accompanied by an increasing interest in the problem of bronchial asthma

The combined influence of members of the I A A can be expected to do much towards achieving a better approach to these problems

Co-operation between sociologists and physicians a co-operation which will have to be intensified during the next few years is particularly essentia in the study of the position in society of patients with chronic allergic disease especially those with bronchial asthma and allergic eczema and to a lesser degree those with severe rhinitis and urticaria

SUMMARY

The Netherlands know the problems of the lower countries with sea climate rivers humidity and the other side heath and woods

Bronchial asthma is found in about 1 p 100 allergic diseases in general in ±30 p 100

No special Dutch allergens seem to exist Extremely important are housedust fungi and infections

Therapy is after intensive examination usually not only anti allergic but also psychosomatic treatment physiotherapy etc In many cases the 7 allergologists work together with other specialists in a team

There is no University teaching in allergology by allergologists but the Neth Society of Allergy has been able to publish several books about allergy topics

Big problems exist with regards to medical examinations for military service and for life—and healthinsurance companies

RÉSUMÉ

Les problèmes des Pays Bas sont ceux de tous les territoires situés aux basses altitudes où le climat est maritime humide les rivières nombreuses ainsi que les landes et les bois

L'asthme bronchique atteint environ 1 p 100 de la population alors que pour l'ensemble des maladies allergiques la proportion est de 30 p 100

Il ne semble pas y avoir d'allergenes specifiques aux Pays Bas Les allergenes les plus communs sont la poussiere domestique les moisissures et les agents d'origine infectieuse

Les therapeutiques employées sont basées non seulement sur la medication anti allergique proprement dite mais aussi sur la physiothérapie et les traitements psycho somatiques

Dans la plupart des cas les sept medecins allergologistes effectuent en collaboration avec d'autres spécialistes un travail d'équipe

Il n'y a pas dans les universités de cours d'allergologie faits par des allergologistes mais la Societé Neerlandaise d'allergologie a pu publier plusieurs ouvrages sur l'allergie

Les examens medicaux avant l'incorporation des militaires et ceux pratiques pour les Compagnies d'Assurance Vie et d'Assurance Sante posent d'importants problemes

ZUSAMMENFASSUNG

Die Niederlande kennen die Probleme der tief gelegenen Lander mit Seeklima Flussen und Feuchtigkeit und andererseits mit Heiden und Walder

In 1 p 100 findet man Bronchialasthma allergische Erkrankungen im allgemeinen in 30 p 100

Es durfte kein eigenes Allergen fur Holland geben Sehr wichtig sind der hausliche Staub Pilze und Infektionen

Nach einer genauen Untersuchung ist die Behandlung nicht nur anti allergisch ausgerichtet sondern auch psychosomatische Therapie Physiotherapie u a werden vorgenommen In vielen Fallen arbeiten die 7 Allergologisten mit anderen Spezialisten in einem Team zusammen

Es gibt keinen Universitatsunterricht von Allergologen uber Allergologie aber die hollandische Allergiegesellschaft war in der Lage einige Bucher uber Allergieprobleme zu veroffentlichen

Grosse Probleme bestehen hinsichtlich der arztlichen Untersuchung fur den Militardienst und fur Lebens und Krankenversicherungsgesellschaften

RESUMEN

En Holanda se presenta el problema de zonas bajas con clima marítimo ríos y humedad y por otra parte landas y bosques

El asma bronquial se encuentra en alrededor del 1 p 100 y las enfermedades alérgicas en general en más o menos el 30 p 100

No existen alergenos típicamente holandeses El polvo doméstico los

hongos y las infecciones son extremadamente importantes Las medidas terapéuticas se deciden luego de una investigación clínica exhaustiva y en general no sólo es anti alérgica sino que se acompaña de tratamiento psico somático psicoterapia etc En muchos casos los 7 alergistas trabajan en equipo con otros especialistas

No hay enseñanza universitaria sobre alergia pero la Sociedad Holandesa de Alergia ha podido publicar varios libros sobre diver os temas de alergia

Existen problemas importantes con respecto a los examenes medico efectuados para el servicio militar y para los seguros

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causes typical hay fever pollen asthma dermatitis and occasior caria There are three typical pollen seasons The first due to c tree pollen starts in April varying in time with the latitude and the and rarely extending beyond the end of May except in more nort gions The most common offenders are from the poplar family t (very commonly planted freely in cities and towns) the maple the the oak In the different regions of Canada one or other type predom In the prairies trees are uncommon except in cities and present no pr The tree season is short usually about five weeks It is intense an cause very severe symptoms Probably the number of cases of tree nosis is less than for grass or weed pollinosis

Grass pollinosis is common and its season usually extends from la May to mid July although some scattered and less abundant sp pollinate all summer and may account for a few late summer cases grasses occur freely in all popul [illegible] and those w are most prevalent include the [illegible] top (Agrostis) and brome grass [illegible] greatly each year with the abundance of air borne pollen which is of cour related to weather conditions Frequent rain may cause a huge growth grass but the moisture causes the thin coated grass pollens to swell f and disintegrate Plantain is widespread across Canada Much of it the common plantain (Plantago major) which produces very little polle and is unimportant clinically The English plantain (Plantago lanceolat occurs in some areas in eastern Canada and may present local problems i midsummer

The most important pollen problem in Canada is that due to weeds It is very common in the large populous eastern or central provinces of Ontario and Quebec i e in the region of the lower Great Lakes and upper St Laurence River In the lower St Laurence region and in the Atlantic provinces the problem is much less but appears to be increasing West of the Great Lakes the weed problem is increasing as it extends northward from the north central United States but decreases as one proceeds westward and is almost non existent west of the Rocky Mountains

The most important weeds are the ragweeds (species include Ambrosia elatior Ambrosia trifida and Ambrosia psilostachya) as well as the marsh [illegible] spp) [illegible] ec [illegible] es [illegible] of [illegible] ne [illegible] in [illegible] the most common and frequent [illegible] ry years is a major

Weed control has made little headway and as the country is opened up with roads and development of greater areas of population the weed problem increases The ragweeds have marched westward from Winnipeg nearly 500 miles in a generation and appear to be continuing Regions such as Port Arthur and Fort William at the western end of Lake Superior once hay fever refuges are now invaded The Russian Thistle accidentally imported into the central plains area of the United States has now spread

northward into Canada where it became exceedingly abundant in the drought years of the 1930's

Mould spores are very plentiful in the air throughout the country The common Saprophytes Alternaria Hormodendrum and Helminthosporium occur widely in the warmer months appearing as soon as the snow leaves the ground and disappearing with the first snow blanket There is also a wide group of spores occurring with little seasonal variation throughout the year including Penicillium the Yeasts Rhizopus Monilia etc Clinical sensitivity is common particularly in the prairie provinces It undoubtedly accounts for the many cases with known hay fever whose symptoms start before the trees pollinate and persist after the frost destroys the weeds and until snow comes in November or December

In agricultural areas most notably the Great Plains pathogenic fungus spores such as rust smut and bunt are very common varying in abundance each year and having a season of about four weeks While these spores are quite allergenic as shown first by Cadham in 1923 and later proven by Wittich in 1937 our experience indicates that less than 10 p 100 of the rural allergic population are affected and the problem is a relatively minor one clinically

Industrial dusts are of course a very important source of allergy Perhaps the most serious of these is grain dust This term is a very general one but as in the case of house dust it is remarkably uniform allergenically Various things in grain dust have been suspect such as saprophytic and pathogenic mould spores but the dust itself seems to be intrinsically allergenic This is borne out by the fact that the crushing of grain as for feed or milling greatly enhances its allergenicity There is a distinct variation in the dusts from wheat barley rye and oats but only in degree and generally sensitivity to one implies sensitivity to all Grain dust allergy causes rhinitis asthma and a particularly severe form of atopic dermatitis It is a serious problem to farmers and to those engaged in the grain trade It is also an important problem near the great shipping grain terminals and mills and citizens of such cities as Fort William and Port Arthur at the head of the Great Lakes often suffer from it even if not engaged in any way in the grain trade Farmers of course also suffer commonly from sensitivity to animal and poultry dust Animals are important environmental problem in homes

Furriers and those engaged in the great fur trade often suffer respiratory and skin allergy

Other industries also present problems to the allergic sufferer and among these I might mention the pulp and paper factories and the smelters both of which produce highly irritant if not allergic gases Smog is an uncommon phenomenon in Canada

Food allergy is relatively common and presents no unusual features Fish sensitivity is probably more common in the Maritimes Due to a highly organized and extensive distribution system most of the population has a highly varied diet and there are few notable seasonal or special food problems Drug sensitivity is becoming more common or more frequently recognized and differs little from that seen elsewhere Penicillin sulphonamides and aspirin continue as major drug allergens

In Canada it is probable that 60 p 100 of respiratory allergy is due to

inhaled and environmental allergens or food The remainder the so called intrinsic cases, have a high degree of infectious factors

The population is becoming highly conscious of allergy and probably is reflecting the popular situation in the U S A Multiple cases in families are common and many people are becoming aware of the hereditary and environmental problems involved Lay interest in allergy seems often to be ahead of that of the general medical profession.

There is a disturbing tendency among phy icians for too frequent use of corticosteroids in allergic cases without adequate effort at simpler and safer management This probably reflects a lack of experienced allergists in the country and a rather uniform neglect of the subject in undergraduate medical education Fortunately more and more systematic teaching of allergy to medical students is appearing and in at least half of our medical schools some formal instruction is now being given and it is expected that more will gradually follow this path

Much of Canada has been carefully surveyed for air borne allergens and more will be done The relationship of climate to allergic disease is often still obscure although climate is too often blamed for a change in the patient s condition when a more rational explanation can often be found in his immediate environment The farmer who is benefitted by moving to the warmer but damper sea level region of the Pacific Coast may only be responding to his removal from grain or animal dust or weed pollen Basic research into the fundamental processes of allergy is going forward chiefly in the laboratories of Dr Bram Rose at the Royal Victoria Hospital and McGill University in Montreal and good clinical research is proceeding in several other centers

SUMMARY

Allergy in Canada is basically much like that found elsewhere in the world and particularly like that of the United States of America Canada s population is mostly white and is made up of large Anglo Saxon and French groups with large Scandinavian, German and Slavic sections There appear to be no allergic differences in the various racial groups

While Canada is very large in area and occupies half of North America its population is largely concentrated along the southern borders which are temperate The high arctic and subartic regions are thinly populated and as vegetation is slight no important air borne allergens occur and the only clinically important allergens are animal and house dust and possibly furs
A [illegible] Shield which occupies
[illegible] ock
a [illegible]
w [illegible] mon
[illegible] May
and important A tree season of five or six weeks occurs in A[illegible] Grasses pollinate abuntantly in June and July The weeds which start to pollinate in late July and persist into September are the major source of seasonal allergy Seasonal and perennial spore sensitivity is common and

chiefly due to saprophytes Rust spores are plentiful and antigenic but are not a major problem clinically

Industrial dusts of various kinds are common allergens and a most notable one is grain dust which is a common serious offender Because of the very cold winters and tightly closed heated buildings house dust is a very common and important allergen

Food and drug allergy are common and present no special or unusual features

Respiratory infections are particularly troublesome in the cold months when frequent epidemic waves occur and bother many asthmatics

The people are becoming very conscious of allergy and its implications Medicine is lagging behind with indifferent education of its students in the subject and a relatively small number of experienced or trained allergists in the country

Research in allergy both clinical and botannical has gone forward in several centers and advanced basic research is proceeding at McGill University in Montreal

RÉSUMÉ

Il n y a pas de difference fondamentale entre l allergie telle qu on la rencontre au Canada, et telle qu elle existe dans les autres pays du monde notamment aux États Unis

La population canadienne est composée d importants groupes ethniques Anglo Saxons et Français avec des apports nombreux de Scandinaves d Allemands et de Slaves Du point de vue de l allergie il ne semble exister aucune différence entre habitants d origines raciales diverses

Territorialement la superficie du Canada est considérable puisqu il represente la moitié de l Amerique du Nord sa population est particulièrement dense le long de ses frontières sud ou règne un climat temperé

Les vastes régions arctiques et subarctiques sont peu peuplées et comme la végétation y est rare on n y rencontre pas d allergenes atmospheriques Les seuls allergènes ayant une importance clinique proviennent des poussieres des animaux domestiques et peut-etre aussi des poils de fourrures Une autre zone tres etendue est comprise entre la formation Pre Cambienne qui occupe une grande partie de la province de Quebec les provinces de l Ontario et du Manitoba C est une region de roches de lacs de cours d eau et de forets de coniferes ou peu de problemes allergiques viennent se poser

Dans les régions habitees et cultivees du Canada le rhume des foins est frequent et son role important La saison du pollen pour les arbres est de cinq ou six semaines en avril et mai Les pollens de graminées sont abondants en juin et juillet Les plantes sont la cause majeure d allergie saisonniere et produisent leur pollen depuis la fin de juillet jusqu en septembre La sensibilisation saisonnière ou permanente aux spores est commune et due principalement aux saprophytes Les spores de la rouille du ble sont abondantes et antigeniques mais ne posent pas de problemes cliniques sérieux

Les poussieres industrielles diverses sont des allergenes communs plus

particulierement la poussiere des grains dont les mefaits sont serieux et fréquents

La poussiere domestique est elle aussi, un allergene frequent et aux effets sérieux du fait que la rigueur du climat oblige les habitants a vivre dans des lieux particulièrement bien clos et chauffes

Les allergènes alimentaires et médicamenteux se rencontrent frequemment mais ne présentent aucun caractère particulier ni inhabituel

Les infections respiratoires sevissent particulièrement pendant les mois les plus froids ou de fréquentes vagues épidemiques apparaissent et viennent s en prendre aux asthmatiques

Le public devient très averti de ce qui touche l allergie et de ses consé quences possibles

La médecine suit avec un certain retard les progres de l allergologie l enseignement medical temoigne pour cette matiere de l indifférence et il n existe dans le pays qu un nombre relativement restreint de medecins ayant reçu un enseignement allergologique et bénéficiant d une experience sérieuse dans cette matiere

Les recherches allergologiques du point de vue de la chimique et de la botanique ont fait des progres dans certains centres et des recherches fonda mentales poussees sont en cours à l Université Mc Gill de Montréal

ZUSAMMENFASSUNG

Die Grundlagen der Allergie in Kanada sind denen der anderen Welt und insbesonders denen der Vereinigten Staaten von Amerika sehr ähnlich Die Bevolkerung von Kanada ist grosstenteils weiss und besteht aus grossen angelsachsischen und franzosischen Gruppen mit skandinavischen deuts chen und slawischen Anteilen Es scheint keinen Rassenunterschied hinsicht lich der Allergie zu geben

Kanada ist flachenmassig sehr ausgedehnt und beinhaltet halb Nordame rika seine Bevolkerung ist stark in den milden Gegenden entlang der sudlichen Grenzen konzentriert Die sehr grossen arktischen und subark tischen Regionen sind nur dunn besiedelt und da die Vegetation nur schwach ist kommen keine wichtigen Luftallergene vor und die einzig klinisch wichtigen Allergene sind tierischer und hauslicher Staub und moglicherweise Pelze Ein anderer sehr grosser Landstrich wird von der Pra Cambrien Zone eingenommen, die grosse Teile von Quebec Ontario und Manitoba umfasst Diese Gegend aus Felsen Wasser und Nadelwal dern zeitigt nur geringe allergische Probleme

In den bevolkerten und kultivierten Regionen von Kanada ist die Pollen krankheit haufig und wichtig Eine Baumsaison uber 5 oder 6 Wochen bes teht im April und Mai Graser bluhen sehr stark im Juni und Juli Die Kräuter beginnen Ende Juli zu bluhen bleiben bis in den September hinein und sind eine sehr wichtige Ursache fur jahreszeitliche Allergien Jahreszeit liche und dauernde Sporenuberempfindlichkeit ist verbreitet und wird hauptsachlich durch Saprophyten hervorgerufen Sporen des Getreide strandes sind reichlich vorharden und antigen stellen aber kein sehr wichtiges klinisches Problem dar

Gewerblicher Staub verschiedener Art ist ein verbreitetes Allergen

besonders erwahnenswert ist der Getreidestaub der als ernstlicher Krankheitsausloser allgemein ist Wegen der sehr kalten Winter und der streng geschlossenen geheizten Hauser ist der hausliche Staub ein sehr verbreitetes und wichtiges Allergen

Nahrung mittel und Medikamentenallergie i t verbreitet und zeigt keine speziellen oder ungewohnlich n Charakteristika

Infektionen der Atemwege sind besonders storend wahrend der kalten Monate wenn haufig Epidemien auftreten und belastigen viele Asthmatiker

Die Bevolkerung ist uber Allergie und ihren Folgen sehr aufgeklart Die Medizin blieb durch eine in diesem Gebiet nur massige Ausbildung der Studenten und wegen einer relativ kleinen Anzahl von ausgebildeten und erfahrenen Allergiefachleuten in unserem Lande etwas zuruck

Allergieforschung sowohl klinische als auch botanische machte in einigen Zentren gute Fortschritte und fortschrittliche Grundlagen forschung wird an der McGill Universitat in Montreal betreiben

RESUMEN

La alergia en el Canada es fundamentalmente igual a la encontrada en otros paises y en particular a la de los Estados Unidos de Norteamerica La población del Canadá es blanca en su mayoria y está formada por anglo sajones y franceses y grupos menores de escandinavos germanos y eslavos Aparentemente no hay diferencias raciales desde el punto de vista alergico

Aunque el Canadá tiene una extensión enorme y ocupa la mitad de la America del Norte su población está concentrada a lo largo de la frontera sur más templada Las zonas árticas y subárticas estan escasamente pobladas y la vegetación es tan poca que no hay practicamente alergenos en el ambiente Los unicos importantes en esas zonas son los pelos de animales el polvo domestico y tal vez las pieles Del mismo modo la región precámbrica que ocupa gran parte de Quebec Ontario y Manitoba rocosa con muchos lagos y rios y bosques de coniferas presenta pocos problemas alérgicos

En las regiones pobladas y cultivadas del Canadá la polinosis es frecuente e importante Hay una estacion de árboles que dura unas seis semanas en abril y mayo las gramineas polenizan abundantemente en junio y julio Las hierbas que comienzan a polenizar a fines de julio y persisten hasta septiembre son las más importantes Es comun la sensibilidad a hongos *especialmente saprofitos estacionales y perennes* Los esporos de ustilago son abundantes pero a pesar de su alergenicidad no constituyen un problema clinico serio

Los polvos industriales de diversa naturaleza son alergenos comunes y un caso notable es el del polvo de cereales que es un factor alergenico importante

La alergia alimenticia y por drogas es frecuente y no presenta características especiales

Las infecciones respiratorias son particularmente molestas en los meses fríos y se producen frecuentes epidemias que agravan a muchos asmáticos

La gente se ha hecho muy consciente de las implicaciones alérgicas La

medicina esta a este respecto en atraso con una deficiente educacion una cantidad relativamente pequeña de especialistas

Las investigaciones alergicas clinicas y botanicas se realizan en vario lugares y un programa de investigaciones básicas está en curso de ejecucion en la Universidad McGill en Montreal

GREAT BRITAIN

by

D A WILLIAMS

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PREVALENCE OF ASTHMA IN ENGLAND AND WALES

Stocks (1949) in a canvassed population of 37 458 persons aged sixteen years and over selected with proper regard to regional distribution and to representation of urban and rural districts found the mean monthly prevalence of asthma from April 1946 to May 1947 to be 0 9 p 100 Asthmatics were included if they had had attacks within two months of being questioned

The General Register Office of England and Wales under the guidance of its Chief Medical Statistician W P D Logan found from the practices of ten general practitioners in England covering a population of 36 889 persons of all ages as indicated by visits to their doctors for this complaint that active asthma between 1951 54 averaged 0 85 p 100 being 0 97 p 100 in 1951 52 0 83 p 100 in 1952 53 and 0 74 p 100 in 1953 54 (Med Pop Sub N° 9 HMSO)

Among young men aged 18 19 years examined for the Army 0 9 % were rejected on account of asthmas (Williams 1951)

In an industrial town Barrow in Furness in North Western England Hamilton and Bendowski (1954) in their practice of 4 000 patients found 1 p 100 consulted them on account of asthma

Grant (1957) in a medical study of 4 571 students (1950 51 to 1953 54 inclusive) in the University of Wales found that 1 9 p 100 had active asthma and 3 3 p 100 had or had had asthma

I T T Higgins of the Pneumoconiosis Research Department Cardiff and myself have recently carried out a survey of the prevalence of asthma in 2 communities in South Wales in a mining valley and in an agricultural area (unpublished) The prevalence of active asthma was 1 4 p 100 in the males and 1 6 p 100 in the females In men (all non miners) there was no significant difference in the prevalence of asthma in the 2 areas In women asthma was more prevalent in the agricultural area

The *prevalence of pollen hay fever* as indicated by patients consulting their doctors is 0 44 p 100 of males and 0 74 p 100 of females The highest prevalence in both sexes is in the 15 44 age group 0 56 p 100 of

males and 0 67 of females (Med and Pop Sub N° 9) Grass pollen is the only accepted common cause of hay fever in Britain tree pollens accounting for some 1,0 p 100 only of all hay fever patients

Urticaria and angioneurotic œdema For all ages the prevalence as measured by patients consulting their doctors is 1 36 p 100 for males and 1 6. p 100 for females The highest figures occur in the 0 14 age group where 3 47 p 100 of males and 3 73 p 100 of females are affected (Med and Pop Subs N° 9)

Eczema and Dermatitis For all ages as measured by patients consulting their doctors eczema occurs in 1 43 p 100 of males and 1 37 p 100 of females The highest figures occur in the 0-14 age group 2 02 p 100 for males and 1 83 p 100 for females but in all age groups the prevalence is over 1 0 p 100 Dermatitis similarly has for all age groups a prevalence of 1 48 p 100 in males and 1 53 p 100 in females with little difference in the sexes or in age groups (Med and Pop Subs N° 9)

INCAPACITY FROM ALLERGIC DISEASES IN ENGLAND AND WALES

In 1953 54 asthma caused a loss of 4 600 000 working days i e 1 6 p 100 of the total days lost from all causes eczema and dermatitis a loss of 2 950 000 days 1 0 p 100 of the total for all causes urticaria 200 000 days and other allergic diseases 40 000 days making a total of 7 790 000 working days lost 2 8 p 100 of the total for all causes This figure of 2 8 p 100 compares with diabetes 0 6 p 100 pneumonia 0 7 p 100 appendicitis 0 9 p 100 duodenal ulcer 1 1 p 100 and gastric ulcer 1 3 p 100 Allergic diseases therefore caused a little more incapacity than duodenal and gastric ulcer combined It is calculated that the cost of sickness payments on account of this group of allergic diseases in 1953 54 was £2 378 000 asthma alone accounting for £1 359 000 (Williams in press)

During 1951 and the year 1953 54 male asthmatic claimants of sick benefit were 6 4 and 6 3 p 10 000 respectively of the working population for females the figures were 7 8 and 8 0 p 10 000 The mean duration of incapacity during 1951 and during 1953 54 for males was 47 0 and 43 5 days and for females 50 4 and 52 1 days Analyses of these official figures showed that it was the middle aged and elderly asthmatics those over 45 years who were specially liable to be off sick on account of asthma and that the least incapacity occured in males in the 25 29 age group and in females in the 30-34 age group A further finding of some interest is that of 9 000 male asthmatics off sick on 5th June 1954 52 p 100 had no worked for 12 months 29 p 100 for over 2 years and 18 p 100 for over 5 years of 4 400 females incapacitated 59 p 100 had been so for over 12 months 50 p 100 for over 2 years and 32 p 100 for over 5 years (Williams in press)

Higgins and I in our survey found that of those with active asthma approximately a half (48 p 100) had no incapacity that just over 35 p 100 were just occasionally incapacitated while some 15 p 100 were frequently incapacitated (i e more than once a month)

DEATHS FROM ASTHMA IN ENGLAND AND WALES

I previously reported that for the period 1930 48 the death rate for asthma in England and Wales averaged 7 1 p 100 000 of the population (Williams 1952) The published figures since that date are shown in Table I These

TABLE I

Deaths from asthma per 100 000 of the population
(Registrar general s Reports 1949 56)

YEAR	1949	1950	195	1952	1953	1954	1955	1956
Males	8 2	7 7	8 8	6 7	6 4	5 9	5 8	5 3
Females	6 3	6 5	7 5	5 4	5 9	5 4	5 1	5 5
Persons	7 2	7 0	8 1	6 0	6 2	5 6	5 4	5 4

figures although showing a downward trend in the last few years are of course higher than those from most other countries and call for a brief comment At Cardiff where there is a population of approximately 300 000 I was able to verify personally during a 5 year period 1951 55 an average of 13 deaths from asthma per year giving a rate of 5 p 100 000 This clinical finding supports the general validity of the Registrar General s figures

If as we have reason to believe from our exceptionally high bronchitis death and morbidity rates (Oswald 1958) we in Britain have a greater tendency to respiratory infection than most countries and then our relatively high asthma death rate may be due to an increased tendency to infective asthma The somewhat lower death rate of recent years may be the effect of antibiotic therapy

attended my clinics are set out in Table II It is interesting that only a small percentage especially in females commence under the age of 5 years and that 70 p 100 have their onset between the ages of 5 and 20 years A comparison of the male and female percentages in age groups shows that female percentage figures similar to those of the male are 5 years later i e in males 40 p 100 under 10 years 60 p 100 under 15 years 85 p 100 under 25 years in females 40 p 100 under 15 years 60 p 100 under 20 years and 84 p 100 under 30 years

Of these 615 hay fever patients 209 or 34 p 100 developed pollen asthma 32 p 100 of the males and 36 p 100 of the females

The *ages of onset and sex of these 209 pollen asthmas* 10_ males and 107

TABLE II

Age of onset of hay fever (grass) in 615 patients

Age	Males No	Males %	Females No	Females %	Males and females No	Males and females %	Male : female ratio
0–4	38	12	18	6	56	9	2 : 1
5–9	88	28	53	18	141	23	1.7 : 1
10–14	63	20	47	16	110	18	1.3 : 1
15–19	39	12	60	20	99	16	1 : 1.5
20–24	43	13	40	14	83	13	1.1 : 1
25–29	21	7	30	10	51	8	1 : 1.4
30–34	12	4	19	6	31	5	1 : 1.6
35–39	8	3	15	5	23	4	1 : 1.8
40–44	4	1	6	2	10	2	1 : 1.5
45–49	2	1	5	2	7	1	1 : 2.3
50–54			2	1	2	—	—
55–59	1		—		1	—	—
60 plus	1				1	—	—
TOTAL	320	101	295	100	615	99	

females are set out in Table III In the same Table are also set out the *ages of onset and sex of* 487 patients (274 males 213 females) with *asthma (unselected)* their only selection being that they were considered undoubted cases of asthma were consecutive patients attending the clinic and resident in Cardiff We have accepted as our definition of asthma those in whom typical recurring spontaneous attacks of dyspnœa and wheeziness

TABLE III

Comparison by age of onset and sex of 487 asthma patients (unselected) and 209 grass pollen asthmatics at Cardiff

Age	Asthma patients (unselected) Male	Female	Male + Female	Grass pollen asthma only Male	Female	Male Female
0–4	50	28 %	40	7	7 %	7
5–9	17	15	16 %	28 %	12	20
10–14	8	6	7	18	7	12
15–24	7 %	8	7	15	26	21 %
25–34	8 %	16 %	11	21 %	26	23
35–44	6	12 %	8 %	9	15 %	9
45–64	4	14 %	8	2	7	3
65 plus		1	—	—	—	—
No of Patients	274	213	487	102	107	209

occured and all were carefully questioned and full examined with ancillary aids whenever indicated

The striking feature is the early age of onset in the males 50 p 100 under the age of 5 years After 25 years of age in males 18 p 100 only developed asthma while in females over 25 years of age 43 p 100 commenced asthma Comparison of these unselected asthmatics with the pure pollen asthmatics shows that under the age of 5 years there are big differences in the percent ages This lends support to our clinical findings that asthma under the age of 5 years is only in a comparatively small percentage dominantly allergic infective and psychological factors being dominant in the majority

AEROBIOLOGICAL INVESTIGATIONS IN BRITAIN

Pollen studies have now been carried out at some 14 stations covering Britain and continuously at Cardiff from 1942 onwards (Hyde and Williams 1953 Hyde 1955)

The average grass pollen count for the season on the gravity slide at Cardiff 1943 56 was 2 097 grains on 1 sq cm During the 14 years con cerned the count varied very widely ranging from 45 5 p 100 of average in 1956 to 146 0 p 100 in 1952 The highest daily count (265 grains on 1 sq cm 14th June 1952) probably corresponded with an atmospheric concentration of 500 grains per cubic metre or more (Hyde 1952 Hyde unpusblished)

Some trees produce significant quantities of airborne pollen most of them in the Spring thus the average annual incidence of oak (Quercus) pollen at Cardiff (which may probably be regarded as typical of southern Britain) is 17 p 100 of grass pollen of birch (Betula) 8 p 100 and ash (Fraxinus) 7 5 p 100 plane trees (Plantanus) are extremely numerous in central London only where the incidence of this pollen may rise to over 110 p 100 of the average grass pollen incidence at Cardiff The flowering seasons of the different trees vary from year to year and their pollen produc tion much more so even the most abundant falling in certain years to below 10 p 100 or even below 5 p 100 of average (Hyde 1956)

Nettle *(Urtica)* is outstanding among herbaceous pollens (weeds) its average annual incidence in some years approaches that of the grasses (Hyde unpublished (a)) In the autumn after the herbaceous pollen season pollen is virtually absent from the air

Mould spores Aerobiological investigations covering most of Britain (Cardiff Llandough London Cambridge Harpenden Southampton Liverpool York and Edinburgh) have shown that 96 p 100 of the catch on culture plates belonged to one or other of 11 genera only 6 of which had a summer predominance viz *Cladosporium* (Hormodendrum) *Pullularia Epicoccum Botrytis Alternaria* and *Candida* By far the most abundant was *Cladosporium* (Hormodendrum) which made up 37 8 p 100 of the total catch *while Alternaria accounted for only 1 0 p 100 (Richards 1954* Hyde Richards and Williams 1956)

Of recent years the gravity slide method of trapping spores has been super seded by the Hirst volumetric spore trap (Hirst 1952) This apparatus catches spores much more efficiently spores of different sizes being caught

almost equally efficiently and it is less affected by wind speeds Basidiospores have been shown to occur in the air in such abundance as to merit serious consideration as allergens (Gregory and Hirst (1952) and one of them Merulius lacrimans (dry rot) has been proven to be antigenic (Frankland and May 1951) Gregory and Hirs (1957) have shown that in the summer hyaline basidiospores (chiefly sporobolomyces) accounted for 31 p 100 of the total catch as against *Cladosporium* 46 p 100 and pollen 1 p 100

INVESTIGATIONS OF ALLERGENS

The detection of allergens is made from the history, skin testing by the prick and or the intradermal methods by trial dieting and by inhalation tests Skin testing is used routinely for the common foods and inhalants while the more unusual allergens are only used if the history is suggestive Skin testing with bacterial extracts in asthma has been disappointing over a limited period in no case have we been able to confirm the clinical significance of a positive skin test by a positive inhalation test Delayed positive skin reactions may or may not have clinical significance in asthma

Inhalation tests have been carried out extensively for a number of years in this country by Herxheimer (1952) and are interesting an increasing number of physicians concerned with asthma Over the last 12 months by the selection of patients with an adequate ventilatory reserve by care with proper dosage and by having isoprenaline solution ready to introduce into the circuit we have found these tests of considerable practical value in confirming or otherwise the role of inhalants such as house dust mould spores and pollen

Undoubtedly the commonest cause of inhalant allergy is house dust Of 396 unselected cases of asthma skin tested by the intradermal method 25 p 100 gave a markedly positive reaction In a group dominantly allergic 50 p 100 gave a markedly positive skin reaction Grass pollen by the prick method in 254 asthmatics gave a markedly positive reaction in 15 p 100 35 p 100 in the dominantly allergic group Feathers is another common inhalant allergen giving a markedly positive skin test by the intradermal method in 11 p 100 of 273 patients and in 23 p 100 of those dominantly allergic Of 627 asthmatics skin tested intradermally with an extract of 1/100 *Cladosporium* (Hormodend
skin reactions in whom a half 4 p
tedly clinically sensitive to *Cladospc*
positive skin reactions of whom only 1 p 100 were adjudged clinically sensitive *Botrytis* was found to be the only cause of clinical sensitivity in some 1 p 100 of patients Mould allergy is undoubtedly a dominant cause of troublesome asthma in some 5 p 100 of patients and may well play a subsidiary part in many more (Hyde Richards and Williams 1956) Pets such as cats dogs horses and birds were only occasional causes of allergic reactions

Food allergy Trial dieting and skin testing to the common foods has been commonly practised for many years *Foods allergy is* commoner in children than adults but it only accounts for a small percentage of allergic reactions Only in individual cases are foods found to be important allergens

ALLERGIC INFECTIVE AND PSYCHOLOGICAL FACTORS IN ASTHMA

Extrinsic allergens have been found in a group of asthmatics of all ages to be the dominant cause of asthma in one third of the cases being of greatest importance in the young adults where it is the dominant cause in over 70 p 100

The infective factor is the dominant cause of asthma in some 40 p 100 of cases and is of special importance in infants and young children and in the middle aged and elderly Many of the very chronic cases are dominantly infective in type The psychological factor appears to be important in just under one third of the cases being of importance in children and in the middle aged and elderly especially the women Often the allergic factor is complicated by the infective factor and psychological factor all three factors occuring together to a lesser or greater degree in approximately one third of all the cases

TREATMENT

Whenever possible removal of allergens is the method of choice Hyposensitization is frequently given for house dust and whenever indicated for pollens and mould sensitive cases Only occasionally is hyposensitization carried out on account of animal danders and only exceptionally for foods

For the common inhalants the methods used are by subcutaneous injection in the way recommended by accepted international authorities (Cooke 1947 Feinberg 1946 Bruun 1956) Grass pollen hyposensitization is usually carried out preseasonally (Frankland 1955) and for many years Perennial treatment is used comparatively infrequently Foci of infection in the sinuses tonsils and teeth are looked for and when necessary dealt with surgically Antibiotics are used in infective cases and when naso respiratory infection recurs Penicillin appears to help some 50 p 100 of cases but many require the wide spectrum antibiotics and sputum cultures and sensitivity tests are helpful Prolonged antibiotic treatment is sometimes necessary Advice is given regarding attention to general health diet warmth and adequate rest to reduce liability to infection Vaccine therapy with a mixed stock vaccine is commonly used

Cortisone and ACTH is being used with proper precautions in all cases of status asthmaticus and increasingly as long term therapy in the chronically affected patient Morphia and pethidine are unnecessary and contraindicated in the treatment of severe attacks

PROFESSIONAL AND EDUCATIONAL

The Asthma Research Council has actively encouraged and assisted research in asthma and allergic problems since its foundation in 19-7 It is supported by public subscription The Medical Research Council and

a number of University Departments have and are sponsoring work on fundamental problems concerned with allergic reactions

The British Association of Allergists was established in 1948 and has just over 100 [illegible] of physicians [illegible] nicians interes[illegible] specialists with a special interest in asthma and other allergic medical problems and dermatologists specially interested in the allergic problems of dermatology Immunologists, chemists and botanists are also among members of our association There are some 40 clinics in Britain that deal specially with allergic problems but in the main, allergy is not recognized as a specialty in itself

The teaching of allergy to medical students is not organised as a special subject nor are there special courses for post graduate instruction However there is a growing realization among the medical profession of the importance of asthma and other allergic diseases in the community and of the importance of allergic reactions in general medicine

I wish to thank my research colleague Mr H A Hyde Keeper of the Department of Botany National Museum of Wales for his assistance with the section on Aerobiological Investigations in Britain and for access to unpublished data I also wish to thank Dr I T T Higgins Pneumoconiosis Research Department Llandough for permission to include data in preparation for publication

SUMMARY

The prevalence of active asthma in the general population has been estimated as from 0 74 p 100 to 1 7 p 100 of the general population Pollen hay fever is around 0 5 p 100 urticaria and angioneurotic œdema around 1 5 p 100 eczema and dermatitis around 1 5 p 100

Incapacity from asthma in 1953/54 caused a loss of some 4 600 000 working days 1 6 p 100 of the total from all causes eczema and dermatitis 2 950 000 days 1 0 p 100 of all causes and when urticaria and other allergic disorders are included the total loss was 7 790 000 working days 2 8 p 100 of the total from all causes The cost of sickness payments is estimated at £ 2 378 000 for 1953/54

The death rate from asthma 1930/48 was 7 1 and 1949/56 was 6 0 per 100 000

Analyses are given of the age of onset and sex of 615 cases of grass pollen hay fever of 101 cases of grass pollen asthma and of 487 cases of unselected asthma patients 34 p 100 of grass pollen hay fever patients developed pollen asthma 70 p 100 of hay fever patients had their onset between 5 and 20 years 7 p 100 of pollen asthma cases commenced under 5 years in comparison with 40 p 100 under 5 years in the unselected asthmatics The relative importance of the allergic infective and psychological factors in asthma in differing age groups is discussed A summary of the aerobiological investigations in Britain is given Grass pollen accounts for almost all cases of pollen hay fever and *Cladosporium* is the commonest mould allergen

Mould spores are the dominant cause of asthma in some 5 p 100 of all asthmatics House dust is the commonest inhalant allergen Foods are comparatively unusual causes of asthma

The methods of investigation and treatment of various allergic illnesses are discussed The British Association of Allergists was established in 1948 and has just over 100 member

RÉSUMÉ

L asthme du a l inhalation d antig nes atteint environ de 0 74 p 100 a 1 7 p 100 du total de la population

Les pourcentages sont de 0 5 p 100 pour le rhume des foins du aux pollens 1 5 p 100 pour l urticaire et l œd me an gio neurotique 1 5 p 100 pour l eczema et les dermatites

L asthme a occasionne pendant la periode 1953 1954 la perte de 4 600 000 journees de travail 1 6 p 100 du total general des journees perdues L eczéma et les dermatites ont fait perdre 2 950 000 jours ou vrables et si l on y ajoute les pertes dues a l urticaire et aux autres maladies allergiques on atteint 7 790 000 journées soit 2 8 p 100 des pertes totales Les frais de maladie sont estimés a £ 2 378 000 pour les annees 1953 1954

Le taux de mortalite pour l asthme a ete pour 100 000 habitants de 7 1 pour les annees 1930 1948 et de 6 0 pour les annees 1949 1956

L auteur analyse l âge de l apparition et la fréquence suivant le sexe sur 615 cas de rhume des foins sur 101 cas d asthme pollinique et sur 87 cas d asthme dont la specificite n a pas eté etablie 34 p 100 des cas de rhume des foins se compliquent d asthme pollinique 70 p 100 des cas de rhume des foins d butent entre 5 et 20 ans 7 p 100 de pol inose apparaissent avant 5 ans alors que dans les cas d asthme non id ntifie 40 p 100 commencent en dessous de cet âge

L auteur discute de l importance relative des facteurs allergiques infec tieux et psychiques dans les differents groupes de malades classes par âge Il rapporte les resultats de recherches aerobiologiques en Grande Bretagne

Les pollens de graminées sont responsables de presque tous les cas de rhume des foins et le *Cladosporium* est le plus commun des allergenes parmi les moisissu es

Pour environ 5 p 100 des asthmatiques les spores des moisissures sont la cause principale de leur maladie La poussiere domestique est le plus fréquent des allergenes inhales Par comparaison les aliments sont assez rarement l origine de l asthme

L auteur discute des methodes de diagno tic et de traitement de diverses maladies allergiques

L Association Britannique d Allergie a ete fondee en 1948 et compte un peu plus de cent membres

ZUSAMMENFASSUNG

Die Haufigkeit der Asthmaerkrankung in der Gesamtbevolkerung wurde auf 0 74 p 100 bis 1 7 p 100 der Gesamtbevolkerung geschatzt An Pollen Heufieber leiden 0 5 p 100 an Urticaria und angioneurotischem Ödem 1 5 p 100 und an Dermatitis 1 5 p 100

Durch Asthma bedingte Arbeitsunfahigkeit verursachte einen Verlust im Jahre 1953/54 von 4 600 000 Arbeitstagen das sind 1 6 p 100 aller Ursachen Ekzem und Dermatitis bedingten den Verlust von 2 950 000 Arbeitstagen das sind 1 0 p 100 aller Ursachen und wenn man Urticaria und die anderen allergischen Storungen mit einbezieht dann betragt der Gesamtverlust 7 790 000 Arbeitstage das sind 2 8 p 100 aller Ursachen Die Kankheitskosten wurden fur 1953/54 auf 2 378 000 £ geschatzt

Die Todesrate auf 100 000 Personen war fur Asthma 1930/48 7 1 und fur 1949 56 6 0

Es wird eine Aufschlusselung von 615 Graspollen Heufieberfallen bezuglich des Krankheitsbeginnes und des Geschlechtes gegeben von 101 Fallen mit Graspollen Asthma und von 487 Fallen von nicht besonders ausgewahlten Asthmapatienten 34 p 100 der an Graspollen Heufieber leidenden Patienten bekamen Pollen Asthma 70 p 100 der Heufieber kranken hatten ihren Krankheitsbeginn zwischen 5 und 20 Jahren 7 p 100 der Pollenasthmafalle begannen unter 5 Jahre vergleichsweise dazu begannen 40 p 100 der nicht naher ausgewahlten Asthmafalle unter 5 Jahren Die relative Bedeutung fur Asthma von allergischen infektiosen und psychologischen Faktoren in den verschiedenen Altersgruppen wird diskutiert Es wird ein Ueberblick uber die aero biologische Forschung in England gegeben Graspollen sind fur die meisten Pollenheufieberfalle verantwortlich und das verbreitetste Schimmelpilzallergen ist *Cladosporium* Schimmelpilzsporen sind die hauptsachliche Asthmaursache bei ca 5 p 100 aller Asthmatiker Der hausliche Staub ist das allgemeinste Inhalations allergen Nahrungsmittel sind zum Vergleich nur ungewohnliche Asthmaursachen

Die Methoden der Erforschung und Behandlung der verschiedenen Allergiekrankheiten werden diskutiert Die britische Allergie Gesellschaft wurde 1948 gegrundet und zahlt nun uber 100 Mitglieder

RESUMEN

La incidencia de asma sobre el total de la población ha sido calculada entre el 0 74 y el 1 7 p 100 Para la polinosis es del 0 5 p 100 para urticaria y edema angioneurotico del 1 5 p 100 y para eczema y dermatitis del 1 5 p 100

En 1953 1954 los dias de trabajo perdidos a causa del asma alcanzaron a 4 600 000 lo que constituye el 1 6 p 100 de los dias perdidos por todas las causas La dermatitis y el eczema ocasionaron una perdida de 2 950 000 dias de trabajo (1 p 100 del total) y si a estas cifras se agregan las producidas por la urticaria y otras enfermedades alérgicas se llega a un total de 7 790 000 dias de trabajo perdidos equivalente al 2 8 p 100 del total Para el periodo citado e calcula que el costo de la atencion medica y gastos de enfermedad ha sido de 2 378 000 de libras esterlinas

La mortalidad por asma fue de 7 1 por 100 000 en 1930/1948 y de 6 0 por 100 000 en 1949/1956

Se presentan cifras de la edad de aparición y sexo sobre 615 casos de polinosis debida a gramíneas sobre 101 casos de asma debida a gramineas y sobre 487 casos de asma no clasificado El 34 p 100 de los pacientes con

polinosis tuvieron asma El 70 p 100 de los pacientes con polinosis tuvieron una edad de aparición entre 5 y 20 años De los casos de asma por polenes el 5 p 100 comenzaron antes de los 5 años en comparacion con el 40 p 100 sobre el grupo de asmáticos no clasificados El autor discute la importancia relativa de los factores alérgicos infecciosos y psíquicos en los diferentes grupos estudiados y se refiere a las investigaciones serobiologicas realizadas en Gran Bretaña

El polen de gramíneas es el responsable de todos los casos de polinosis y el alergeno micótico más frecuente es el *Cladosporium* El numero de casos de asma producido por esporas de hongos alcanza al 5 p 100 del total Entre los inhalantes el polvo domestico es el más importante Los alimentos son causa poco frecuente de asma

El autor discute los metodos de diagnóstico y tratamiento de las diversas enfermedades alergicas La Asociación Británica de Alergistas fue fundada en 1948 y cuenta con algo más de 100 miembros

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SYMPOSIUM II

Propriétés physico chimiques des anticorps allergiques
Physico chemical properties of allergic antibodies
Physiko chemische Eigenschaften der allergischen Antikorper
Propiedades fisico quimicas de los anticuerpos allergicos

SYMPOSIUM III

Acquisitions recentes sur l étiologie et le traitement des affections allergiques
Recent advances in some phases of clinical allergy
Neue Ergebnisse uber die Aetiologie und die Behandlung der allergischen Krankheiten
Recientes adelantos en la etiologia y tratamiento de las enfermedades alérgicas

SYMPOSIUM IV

Aspects biochimiques de l'hypersensibilité
Biochemical aspects of hypersensitivity
Biochemische Anschaungen der Überempfindlichkeit
Aspectos bioquímicos de la hipersensibilidad

SYMPOSIUM V

Auto et iso sensibilisations
Auto and iso immune reactions
Auto und iso immunitive Reaktionen
Auto e iso sensibilizaciones

SYMPOSIUM VI

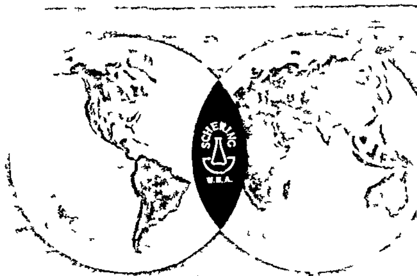
L eczema diathésique
Atopic dermatitis
Atopische Dermatitis
El eczema diatésico

SYMPOSIUM VII

L allergie et son retentissement social dans les différents pays
Allergic management and problems in different parts of the world
Die Allergie und ihre soziale Auswirkung in den verschiedenen Ländern
Repercusiones sociales de la afecciones alérgicas en diferentes paises



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